Innovation in home mechanical ventilation

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The research in this thesis was financially supported by: Health Care Insurance Board in the Netherlands, the University Medical Center Groningen, Vivisol Area UK & Benelux and ResMed Benelux.
The publication of this thesis was financially support by: University of Groningen, the University Medical Center Groningen, Vivisol Area UK & Benelux and ResMed Benelux.

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Author: Anda Hazenberg
Cover design and lay-out: Jans Nijboer
Printed by: Scholma Print & Media, Bedum

ISBN: 978-90-367-9324-7 (printed version)
ISBN: 978-90-367-9323-0 (electronic version)

rijksuniversiteit
groningen

Innovation in home mechanical ventilation

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 8 maart 2017 om 16.15 uur

door

Andrea Hazenberg

geboren op 13 maart 1962

te Wieringermeer

Promotores
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Prof. dr. H.A.M. Kerstjens

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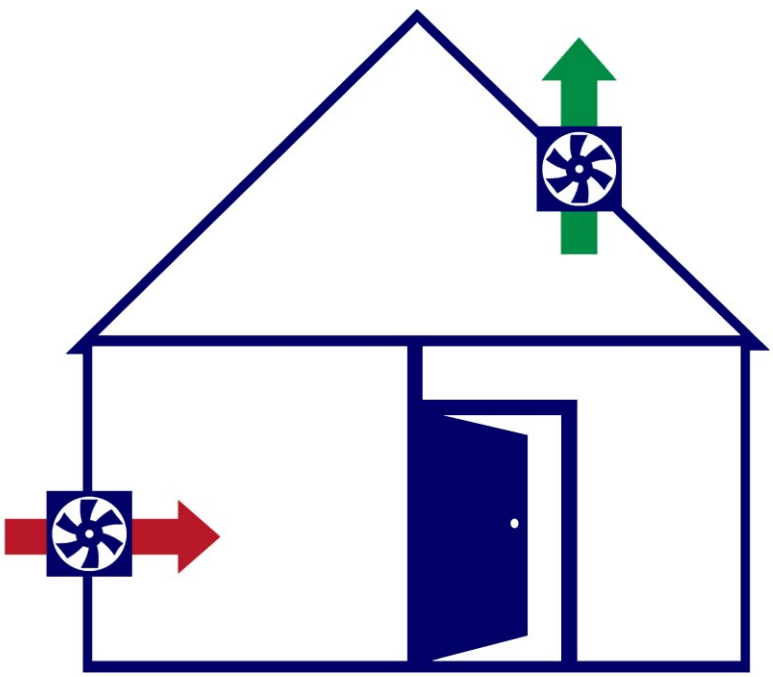
Chapter 1

General introduction



GENERAL INTRODUCTION

Home mechanical ventilation

The start of home mechanical ventilation (HMV) was in fact the result of the polio epidemic in 1950. During this epidemic patients needed ventilatory support and intensive care units had to be set up. As these patients needed ventilatory support sometimes continuously and no other medical need for staying in the hospital was present, HMV was started. While it took many years to start HMV in the Netherlands, the last decades we see an enormous growth in the number of patients on HMV. In 1991 there were 200 patients on HMV and this has increased to almost 3000 in 2015 [1]. The primary goal of HMV is to improve quality of life by reducing the signs and symptoms of chronic hypoventilation. Reduction of the carbon dioxide (pCO_2) concentration in the blood, especially at night, is essential, and hypoxemia improves at the same time. Hypoventilation, by muscle weakness or reduced mobility of the thoracic cage, can cause a number of complaints such as; poor sleep quality, sudden awakenings with a panic sensation, headache upon awaking, spontaneous dyspnoea at night, concentration problems, drowsiness and decreased appetite. These complaints disappear after the start of HMV [2]. Home mechanical ventilation (HMV) is an effective treatment specifically in patients with a neuromuscular disease or a thoracic cage problem combined with daytime hypercapnia [2-4]. Examples of these neuromuscular diseases include diaphragm paralysis, Duchene muscular dystrophy, myotonic dystrophy, limb girdle dystrophy, fascioscapulohumerale dystrophy, amyotrophic lateral sclerosis (ALS) and others. Examples of a restrictive disorders caused by a thoracic cage problem are kyphoscoliosis and obesity hypoventilation syndrome. HMV further developed due to a rapid technical progress in ventilators and wheelchair technology, improving patients' mobility and participation in life, making the option of HMV more attractive. The change from invasive to non-invasive positive pressure ventilation starting in the 1980s also contributed to the 10% growth we see in the Netherlands every year [1,5]. Currently, HMV is judged as an effective treatment as it can improve both survival and quality of life [6-9].

Respiratory failure

Respiratory failure is a condition in which the respiratory system fails to exchange carbon dioxide and oxygen. Pathophysiological, respiratory failure can be divided into two types. Hypoxemic respiratory failure, type I, is characterized by an arterial oxygen tension of < 8.0 kPa with a normal carbon dioxide tension. Hypercapnic respiratory failure, type II, is characterized by an arterial carbon dioxide tension of > 6.0 kPa. Respiratory failure can occur

as acute, chronic or acute-on-chronic. HMV is the treatment of choice in case of hypercapnic respiratory failure.

Hypercapnic respiratory failure in neuromuscular disease

Patients with neuromuscular diseases comprise a heterogeneous group, which includes many uncommon diseases [10]. In this group of patients the ventilatory pump is no longer sufficient due to muscle weakness, leading to an increase in pCO_2. Sometimes the patient is not aware of these symptoms as he or she gradually adjusts to this situation and does not feel impaired. Therefore, patients with a neuromuscular disease need to be monitored to detect symptoms of hypoventilation early, especially during the night, as hypoventilation will start first in this situation. Monitoring can start also by assessing vital capacity (VC). If the VC drops below 60% it should be followed with repetitive measurements of spirometry to evaluate the progression of the disease. Hypoventilation is usually seen when VC < 40% of predicted and once VC drops < 25% at daytime, hypercapnic respiratory failure occurs [11]. Diaphragm paralysis caused by spinal cord injury, thoracic surgery or neuralgic amyotrophy is also part of this group. In case of unilateral diaphragm paralysis there is often no hypercapnic respiratory failure, but the orthopnoea can nevertheless be a reason to start HMV in these patients.

Hypercapnic respiratory failure in restrictive thoracic disorders

Various etiologies, causing deformities of the thoracic cage, lead to restrictive thoracic disorders, characterized by reduced thoracic cage compliance [12,13]. In patients with a restrictive thoracic cage disorder the respiratory muscles are at a mechanical disadvantage due to their suboptimal contraction length. This causes an ineffective interaction between the respiratory muscles and the thoracic cage, and increases the inspiratory muscles load leading to respiratory failure [14].

Monitoring of respiratory failure

Transcutaneous monitoring

The measurement of oxygen and carbon dioxide is used to monitor the respiratory status of a patient. The “gold standard” is still the analysis of arterial blood samples, however, this an invasive procedure. In 1960 Severinghaus was the first to look for a non-invasive method to measure carbon dioxide on the human skin surface [15]. Non- invasive measurement of transcutaneous carbon dioxide by local heating of the skin tissue through a sensor, has been tested in several settings [16-19]. They all showed that transcutaneous monitoring can replace the arterial sampling of carbon dioxide with clinically acceptable accuracy in adults with chronic respiratory failure using mechanical ventilation.

Telemonitoring

Dutch regulations for HMV demand initiation of ventilatory support in the hospital. However, especially disabled patients with a personal tailored care system at home are frequently not satisfied with the level of care in the hospital. In these circumstances telemonitoring could be considered to monitor patients' status at distance. In other diseases telemonitoring allows reduction of chronic disease complications, provides health care services without using hospital beds and reduces patient travel time, time off work and overall costs [20]. Telemonitoring at home in case of HMV would need transmittal of data of the mechanical ventilator and the transcutaneous monitor of oxygen saturation and carbon dioxide pressure. In this thesis the initiation of non-invasive ventilation outside the hospital by using telemonitoring is described.

Treatment of respiratory failure

Non-invasive ventilation

Currently the most used form of HMV is non-invasive ventilation (NIV), which is mechanical ventilation administered via a nasal, mouth-nasal, full face mask or mouthpiece. The use of NIV has markedly increased over the past two decades and has now become an integral tool in the management of both acute and chronic respiratory failure, in both the home setting and in the hospital [21]. Invasive ventilation is only used in 15-20% of the HMV population in the Netherlands.

Improvements in symptoms and daytime arterial blood gas tensions are consistently seen in patients with HMV [22] (table 1). There are three different theories how NIV might improve alveolar ventilation and gas exchange. The first is that the respiratory muscles rest during NIV [23,24]. The second theory is resetting the pCO_2 [25] which means that ventilation will get more responsive to an increase in pCO_2. Finally changes in the pulmonary mechanics after the start of NIV might result in an increased respiratory muscle strength and re-expansion of areas of atelectasis [26]. A recent study in patients with a restrictive thoracic disorder showed that the increased ventilatory response to carbon dioxide after the initiation of NIV is probably the most important contributor [14].

Table 1. Effects of chronic non-invasive positive pressure ventilation [21].

Short term effects	**Long-term effects**
Increased ventilation	Improved exercise capacity
Reduced work of breathing	Improved sleep duration and quality
Improved blood gasses	Increased quality of life
Increased strength and endurance of respiratory muscles	Reduced hospitalization rates
	Prolonged survival

Diaphragm pacing stimulation

Another more experimental therapy is diaphragm pacing primarily used in patients with a Spinal Cord Injury (SCI). In case of high cervical spinal cord injury this is mostly invasive for 24 hours a day. Diaphragm pacing is a technique in which the diaphragm is stimulated by an external pacemaker [27]. By electrical stimulating the diaphragm the muscle contracts, moves down creating under pressure in the thoracic cage, and allowing air to be sucked into the lungs. After this inspiration, exhalation follows the moment there is no stimulus. Diaphragm pacing might by an attractive alternative as it can replace non-invasive or even invasive ventilatory support, while it increases the mobility of the patient.

Aims and outline of this thesis

Ever since the 1950s when poliomyelitis patients were helped by chronic ventilatory support there has been a need for better techniques to transfer care from the hospital to the home environment. The overall topic of this thesis is innovation in the field of chronic ventilatory support with regard to both diagnosis and treatment.

In **chapter 2** we describe the situation of home mechanical ventilation in the Netherlands from the start until now.

Chapter 3 shows the results of the validation of a transcutaneous carbon dioxide monitor compared to the golden standard being the assessment of carbon dioxide from arterial blood.

In **chapter 4** we present the results of our randomized controlled trial to investigate if initiation of chronic ventilatory support at home is as effective as initiation in the hospital (EOLUS).

In **chapter 5**, a post hoc analysis on the EOLUS data focusing on differences in outcome between ALS and non-ALS patients is presented.

In **chapter 6** the reason for the institution of a data safety and monitoring board in the EOLUS study and advice for high risk, investigator initiated studies is discussed.

Diaphragm pacing as an alternative for chronic ventilatory support is presented in **chapter 7**.

Chapter 8 comments on the lack of efficacy of diaphragm pacing in patients with amyotrophic lateral sclerosis. We describe how spirometry assessed while the patient is in different positions can be helpful to evaluate diaphragmatic function in **chapter 9** and when a drop in vital capacity is present to consider that chronic ventilatory support can be effective in **chapter 10**.

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Chapter 2

Home mechanical ventilation in the Netherlands

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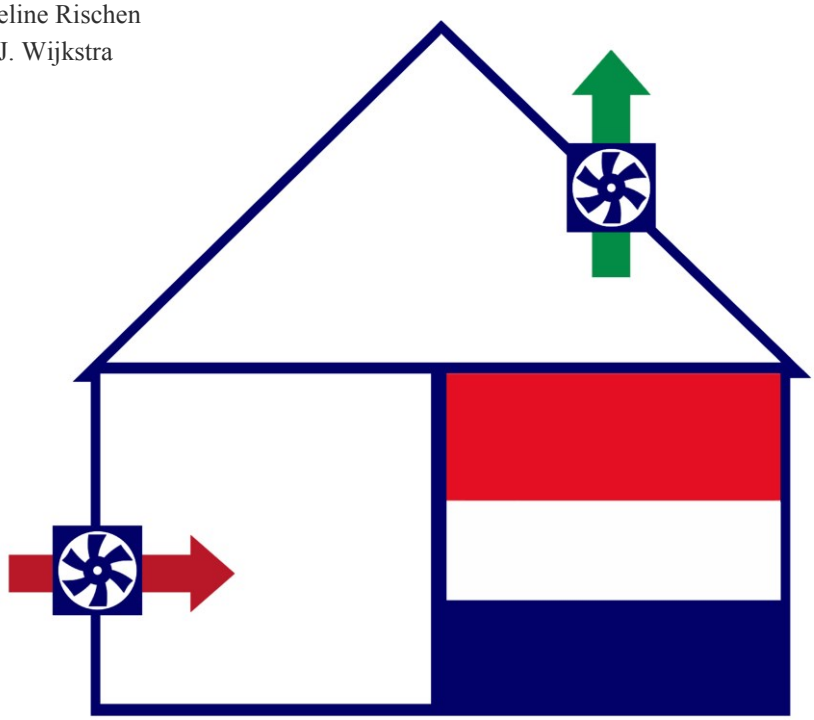


Adapted from:
Nederlands Tijdschrift voor Geneeskunde 2012; 156: A3609

Main points

- The number of Dutch patients with home mechanical ventilation increased from 200 to 2000 over the last 20 years.
- Home mechanical ventilation is a cost effective treatment that significantly improves quality of life.
- Eighty three percent of the patients with home mechanical ventilation lives at home.
- An extra growth is to be expected of patients with obesity hypoventilation syndrome and a new potential group of patients with chronic obstructive pulmonary disease (COPD).
- Strict regulations are necessary to ensure safety in the complex care that entails home mechanical ventilation.

Introduction

A patient with home mechanical ventilation is dependent on a mechanical ventilator, usually for the rest of their life. In the Netherlands home mechanical ventilation started in 1960. As a spin off after the poliomyelitis epidemic, in the 50's, a large group of patients had become dependent on long-term mechanical ventilation [1]. In the 80's non-invasive positive pressure ventilation started (NPPV) [2,3]. This way of ventilatory support uses a mask over nose and or over mouth of the patient (figure 1). Correct ventilator settings ensure an increase in ventilation which improves gas exchange.

Figure 1.

a **b**

Choice of masks; a = full face mask; b = nasal mask

The last 20 years the number of patients with home mechanical ventilation is registered by the 4 centres of home mechanical ventilation (HMV), in Groningen, Maastricht, Rotterdam and Utrecht. In 1991 there were 200 of these patients in Netherlands, in 2011 this number increased to 2000.

In this article we will provide more information about HMV because it is the expectation that more and more health care providers will be confronted with patients on HMV. The indications

and the results, especially the effect on quality of life, after starting with HMV will be highlighted.

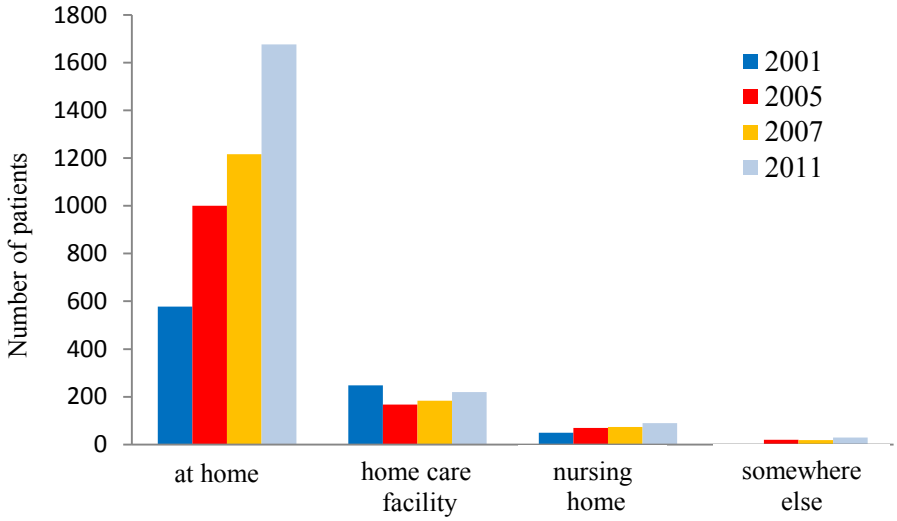
Aim of home mechanical ventilation

The primary goal of HMV is to improve quality of life by reducing the signs and symptoms of chronic hypoventilation. Reduction of the carbon dioxide (pCO_2) tension in the blood, especially at night, is essential, while hypoxemia (pO_2 < 9.5 kPa) will improve as well. Hypoxemia alone is not an indication to start HMV.
Hypoventilation, caused by muscle weakness or thoracic cage problems, causes a number of complaints like; general malaise, headache upon awakening, nightmares, spontaneous dyspnoea at night, concentration disorders, drowsiness and decreased appetite. Sometimes the patient is not aware of these symptoms as he or she has gradually adjusted to this situation and does not sense the impairment.

Publications

Various studies have shown that HMV is effective by improving quality of life, functional status and survival [4-9], normally by improving gas exchange.
A recent study showed that after starting HMV in 85 patients, regardless of the underlying diagnosis, quality of life improved significantly [5]. In this study the Severe Respiratory Insufficiency (SRI) questionnaire was used. The SRI was developed to detect an improvement in quality of life in patients with chronic respiratory insufficiency. It showed a significant and clinically relevant improvement after 1 month of HMV; while after 1 year this improvement was still present.
Another study showed that the social and mental functioning of patients improved after starting HMV and that they had an increased vitality and better cognition [6]. In patients with Duchenne muscular dystrophy the endurance capacity of the ventilatory muscles improved after starting with HMV [7].
HMV also has a positive impact on survival, as shown in 2 Dutch studies. In patients with Duchenne muscular dystrophy, 5 years after starting HMV, 70% was still alive while 70% of the patients with post-poliomyelitis syndrome was still alive after 10 years [8,9]. In addition HMV not only reduced the number of hospitalizations, it was also cost effective [10]. Finally, the fact that in the Netherlands today 83% of patients with HMV lives at home, suggest that HMV has also a positive effect on the quality of life and physical functioning (figure 2) (www.vsca.nl).

Figure 2.



Place of residence of patients with home mechanical ventilation in the Netherlands

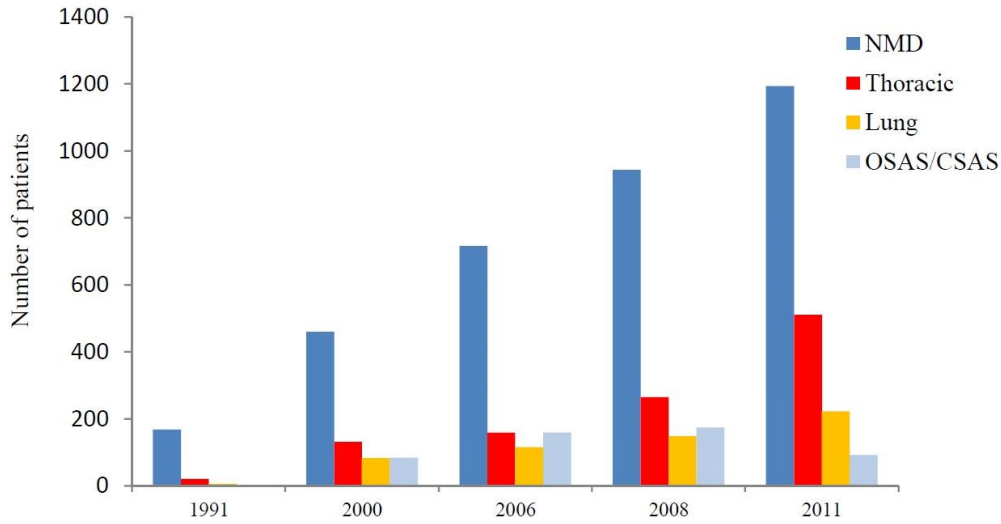
Indications for HMV

Patients eligible for HMV can be divided into 4 groups (figure 3). The first group includes patients with a neuromuscular, central or peripheral nervous system disorder. Examples are patients with muscular dystrophy (Duchenne muscular dystrophy, for example), amyotrophic lateral sclerosis (ALS), spinal cord injury or a diaphragm paralysis.

The second group consists of patients with a thoracic cage problem, for example congenital kyphoscoliosis. The obesity hypoventilation syndrome also belongs in this group, as the obesity has a negative effect on the mobility of the thoracic cage. The latter diagnosis is valid if patients fulfil all following criteria; a BMI > 30 kg/m2, an arterial pCO_2 > 6.0 kPa (45 mmHg) while the hypercapnia cannot be explained by another condition than the obesity.

The third group entails patients with lung diseases. No consensus exists currently in the Netherlands regarding HMV in patients with chronic obstructive pulmonary disease (COPD). Patients who are on the waiting list for lung transplantation, for example patients with cystic fibrosis, are eligible for HMV as bridge to transplantation.

The fourth group are patients with sleep related breathing disorders, like obstructive sleep apnoea syndrome (OSAS) and central sleep apnoea syndrome (CSAS). If continuous positive airway pressure (CPAP) is not effective, HMV might be an option.
Figure 3.



Indication for home mechanical ventilation and numbers of patients over the last 20 years; NMD: neuromuscular disease; Thoracic: thoracic cage problem; Lung: lung diseases; OSAS: obstructive sleep apnoea syndrome; CSAS: central sleep apnoea syndrome.

Initiation of HMV

In 2010, the 4 HMV centres developed criteria to define when patients should be referred. This is published on the website of the Dutch organization; Vereniging Samenwerkingsverband Chronische Ademhalingsondersteuning (www.vsca.nl). Last year HMV in the Netherlands was initiated in 531 patients in the 4 centres either an intensive or- medium care unit or a ward with specific expertise.
At this moment a study is performed in which patients with a neuromuscular disorder or a thoracic cage problem start HMV at home. In 51 of the 55 participants the initiation was successful (unpublished data). Another study resulted in a success rate of 85%, however this was in patients with COPD in a clinical setting [11]. The use of the optimal equipment and appropriate mask is crucial, it takes time and needs individual attention [5]. The centres of HMV have enough expertise to guide the patient professionally during the entire process of HMV.

Experiences in different diagnoses

Duchenne muscular dystrophy

Nowadays non-invasive ventilatory support in patients with Duchenne muscular dystrophy is the most frequent application of HMV and therefore the number of patients that needs a tracheostomy over the last 10 years has decreased from 40% to 19%. In patients with HMV using a mask during the night and a mouthpiece during daytime, survival increased; HMV by mouthpiece is safe for most of these patients [12]. A recent Belgian study has shown that the workload of the respiratory muscles during the day can be reduced if patients were ventilated during the day by mouthpiece in combination with mask ventilation during the night [7].
Patients with Duchenne muscular dystrophy using HMV experienced the possibility to lead an independent life. The quality of life increased from the start with HMV by improving sleep quality and reducing the complaints caused by hypoventilation. It was striking that the score for quality of life in these patients was similar in many domains compared to the healthy population. Patients who were ventilated, being in an advanced stage of the disease, scored about as high on quality of life as patients with Duchenne muscular dystrophy that did not start HMV [13]. Additionally survival increased with 5 to 10 years after starting with HMV [14].

Amyotrophic lateral sclerosis

The number of patients with amyotrophic lateral sclerosis (ALS) in the Netherlands that started with HMV increased from 62 in 2008 to 113 in 2010. These patients chose for HMV partly because a randomized study showed that HMV improved quality of life and survival significantly [15]. In the group of patients with non-bulbar ALS, the median survival was 205 days longer than in the group without HMV. However, patients with bulbar ALS showed no significant improvement in survival and quality of life.
What to do when non-invasive ventilatory support is no longer effective?
In progressive diseases, it is important that before HMV is initiated, patients and caregivers consider what to do when non-invasive ventilatory support is no longer effective. Careful alignment with the general practitioner and other care givers is important to anticipate the worsening clinical situation that is definitely going to occur. In that context it is recommended in conjunction with the primary responsible physician, to provide an adequate medical treatment, in case of shortness of breath or when HMV is no longer effective. Palliation of dyspnoea is often treated with morphine or midazolam. Some patients choose for euthanasia.
If the patient chooses for HMV, this is usually for the rest of their life and this has consequences for the care at home, among a possible infringement on the privacy. If enough care at home cannot be provided for, admission in a nursing home may be necessary. For many

patients, however, this is not a real option. For this reason, and since admission capacity for HMV patients in nursing homes is low, only few patients receive HMV outside their own place of residence.

Discharge and care at home

Discharge can only take place when safety of home mechanical ventilation is guaranteed. The patient and all health care providers receive instructions on how to use the equipment, are informed about the possible alarms and the actions that have to be taken in case problems occur. On the day of discharge, the patient is visited at home by a specialized nurse and the equipment will be installed. The department of HMV can be contacted 24/7 and is always available in case of problems. At least once a year, both oxygen saturation and carbon dioxide during the night will be checked while the patient is being ventilated and when necessary this will be done more often. Also, at least once a year the patient will visit the outpatient clinic of the HMV centre.
The general practitioner (GP) is the primary responsible physician for patients with HMV and the first to contact in case of problems. The activities and the role of the GP depends of the stage of invalidity and the progression of the underlying disease. Especially in the final stage of the disease, a big effort is asked of the family, caregivers, professionals and the GP to provide comfort [16].

Future

The World Health Organization expects that by 2015, 2.3 billion people will be overweight, of whom 700 million with obesity. It is expected that the number of patients with obesity hypoventilation syndrome increases and therefore consequently the need for HMV [17,18]. Research in this group has shown that within one month after the initiation of HMV improvements in gas exchange occur. Also morning headache, dyspnoea and daytime sleepiness disappear.
The second group that is eligible for HMV, are patients with COPD. After a long period in which the effect of HMV in this group was under discussion, there are now indications that HMV could be effective in patients with COPD and a high carbon dioxide level [19]. Even improvement in the forced expiratory volume in one second (FEV1) was demonstrated [20,21]. A recent Dutch randomized controlled study confirmed these results and reported an improvement in quality of life, 3 months after the initiation of HMV. In this study, rehabilitation was combined with HMV during the night, while the control group received only rehabilitation [11].

The last years there was an increase in patients who need more complex care. This development creates an extra demand for facilities for this group of patients, such as nursing homes and home care organizations. Because these patients can only survive by continuous ventilatory support (24/7), safety aspects are crucial. This creates increased demands of the organizations in combination with more stringent safety requirements for the complex care around these patient. Recent European research shows that the quality of care around HMV is significantly better in centres treating more patients [22]. It is therefore preferable to offer HMV primarily by designated centres of home mechanical ventilation. The expectation is that the number of patients with an indication for chronic ventilation will increase. We expect that the average growth of 10% a year that we saw over the last 20 years will continue. This growth in combination with a further increase of complex patients means that HMV can only be guaranteed if all parties involved in health care are willing to contribute maximally.

Learning points

- Home mechanical ventilation is an effective treatment in patients with a neuromuscular disease and thoracic cage problem and saves costs.
- The last 10 years, there is a continuous growth in the number of patients with HMV, 81% of them receive non-invasive ventilatory support.
- The increased complexity of care requires strict regulation to ensure the safety of patients with HMV.
- Because of the expected growth of patients with obesity hypoventilation syndrome and the potential new group of patients with chronic obstructive pulmonary disease, the need for HMV will further increase.
- The quality of care in patients with HMV is best in centres providing home mechanical ventilation to a large group of patients.

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Chapter 3

Validation of a transcutaneous CO_2 monitor in adult patients with chronic respiratory failure

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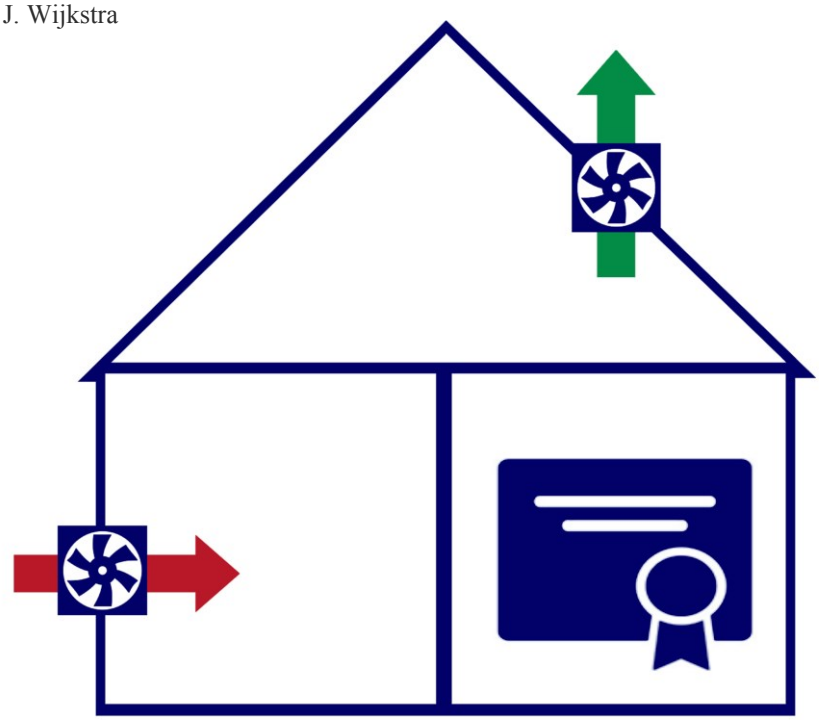


Adapted from:
Respiration 2011; 81:242–246

Abstract

Background

Home mechanical ventilation is usually started in hospital as arterial blood gas sampling is deemed necessary to monitor CO_2 and O_2 adequately during institution of ventilatory support. A non-invasive device to reliably measure CO_2 transcutaneously would alleviate the need for high care settings for measurement and open the possibility for home registration.

Objectives

In this study we investigated whether the TOSCA® transcutaneous CO_2 ($PtcCO_2$) measurements, performed continuously during the night, reliably reflect arterial CO_2 ($PaCO_2$) measurements in adults with chronic respiratory failure.

Methods

Paired measurements were taken in 15 patients hospitalized to evaluate their blood gas exchange. Outcomes were compared 30 min, 2, 4, 6 and 8 h after attaching the sensor to the earlobe. A maximum difference of 1.0 kPa and 95% limits of agreement (LOA) of 1 kPa between CO_2 pressure measurements, following the analysis by Bland and Altman, were determined as acceptable.

Results

Mean $PtcCO_2$ was 0.4 kPa higher (LOA –0.48 to 1.27 kPa) than mean $PaCO_2$ after 30 min. These figures were 0.6 kPa higher (LOA –0.60 to 1.80 kPa) after 4 h, with a maximum of 0.72 kPa (LOA 0.35 to 1.79 kPa) after 8 h. The corresponding values for changes in $PtcCO_2$ versus $PaCO_2$ were not significant (ANOVA).

Conclusions

$PtcCO_2$ measurement, using TOSCA®, is a valid method showing an acceptable agreement with $PaCO_2$ during 8 h of continuous measurement. Therefore, this device can be used to monitor CO_2 adequately during chronic ventilatory support.

Introduction

Home mechanical ventilation (HMV) is an effective therapy which improves survival in patients with chronic respiratory failure due to neuromuscular disease and chest wall deformation [1,2]. Recent guidelines describe when to start with HMV [3]. In general, a combination of symptoms such as fatigue, headache, dyspnoea and respiratory failure (arterial CO_2, $PaCO_2$, >6.0 kPa) suggests that ventilatory support is indicated. Usually HMV is started clinically as arterial blood gas sampling is necessary to confirm the diagnosis and monitor CO_2 and O_2 adequately during initiation of ventilatory support. Arterial cannulation is, however, an invasive and painful procedure with occasional complications including infection, vascular damage and thrombosis [4]. Especially in this group of patients, severe deformities sometimes make the procedure technically challenging. In many hospitals patients have to be admitted to the intensive care unit (ICU) for logistical reasons, leading to higher costs and occupation of a scarce facility. Home monitoring in patients with non-invasive ventilation or long-term oxygen therapy is therefore an interesting alternative as was shown recently [5,6]. The possibility to non-invasively and reliably monitor carbon dioxide in combination with oxygen saturation would lead to an enormous improvement of patient care and probably reduction of costs. In recent years, transcutaneous measurement of CO_2 has become available and several different devices have been tested. While Storre et al. [7] used the SenTec digital monitor, Janssens et al. [8] showed that transcutaneous carbon dioxide ($PtcCO_2$) can be measured with the Radiometer TCM-3 capnograph during 8 h and a sensor temperature of 43°C without recalibration. The TOSCA® monitor was used in both the acute setting of non-invasive ventilation for exacerbations of COPD [9] and during cardiopulmonary exercise testing [10]. Transcutaneous monitors have been evaluated in many settings like anesthetized children [11], critically ill adults [12], during major surgery [13], in newborns [14] and in sleep studies [15]. However, until now no study has investigated whether the TOSCA® $PtcCO_2$ monitor is a valid tool to monitor carbon dioxide gas exchange continuously without replacing the sensor during 8 h. In this study we investigated whether $PtcCO_2$ measurements, using the TOSCA® $PtcCO_2$ monitor continuously during the night, adequately reflect arterial blood gas assessments in adults with chronic respiratory failure.

Methods

The TOSCA® $PtcCO_2$ monitor is a device which non-invasively assesses CO_2 levels in combination with standard pulse oximetry. The Institutional Review Board of our university approved this study. Informed consent was obtained from all participants prior to study inclusion. The $PtcCO_2$ monitor is attached to the patient's earlobe via a sensor and disposable clip. It warms the lobe to 42°C allowing arterialization of capillary blood and measures CO_2 using a Stow-Severinghaus-type electrode [16]. $PtcCO_2$ is measured by determining the pH of an electrolyte solution that is situated between the sensor and a Teflon membrane.
Validation of the TOSCA® $PtcCO_2$ monitor was assessed by comparing $PtcCO_2$ by TOSCA® with $PaCO_2$ in 15 consecutive patients. All patients were either using chronic ventilatory support or were expected to commence it in the near future. All patients were admitted to the ICU for invasive blood gas monitoring to evaluate their nocturnal gas exchange. Heparinized arterial blood gas samples were drawn from an arterial line every 2 h and analysed on the blood gas analyser ABL715 (Radiometer Medical ApS, Brønshøj, Denmark). Paired samples were taken from the radial artery and compared with transcutaneous monitor readings every 2 h. Thirty minutes after the sensor was attached, the first $PtcCO_2$ was determined, while at the same time the first arterial sample was taken. Subsequent paired measurements were taken at 2, 4, 6 and 8 h. Although the TOSCA® device presents continuous readings, only the paired samples with the same interval as the arterial blood gas samples were used for the analysis.

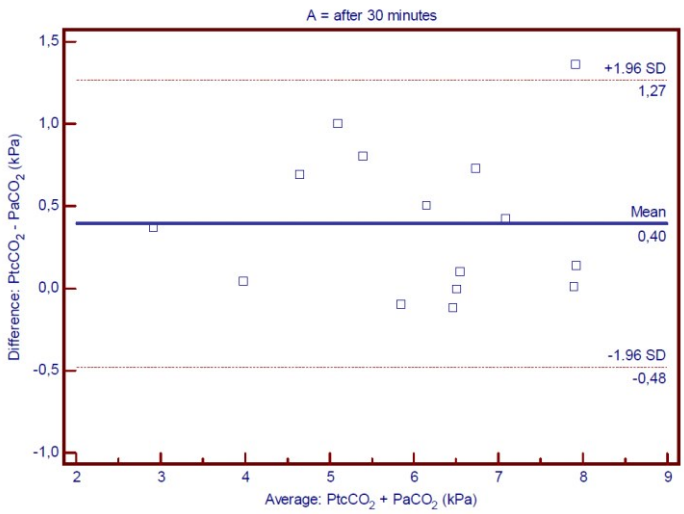
Statistical Analysis

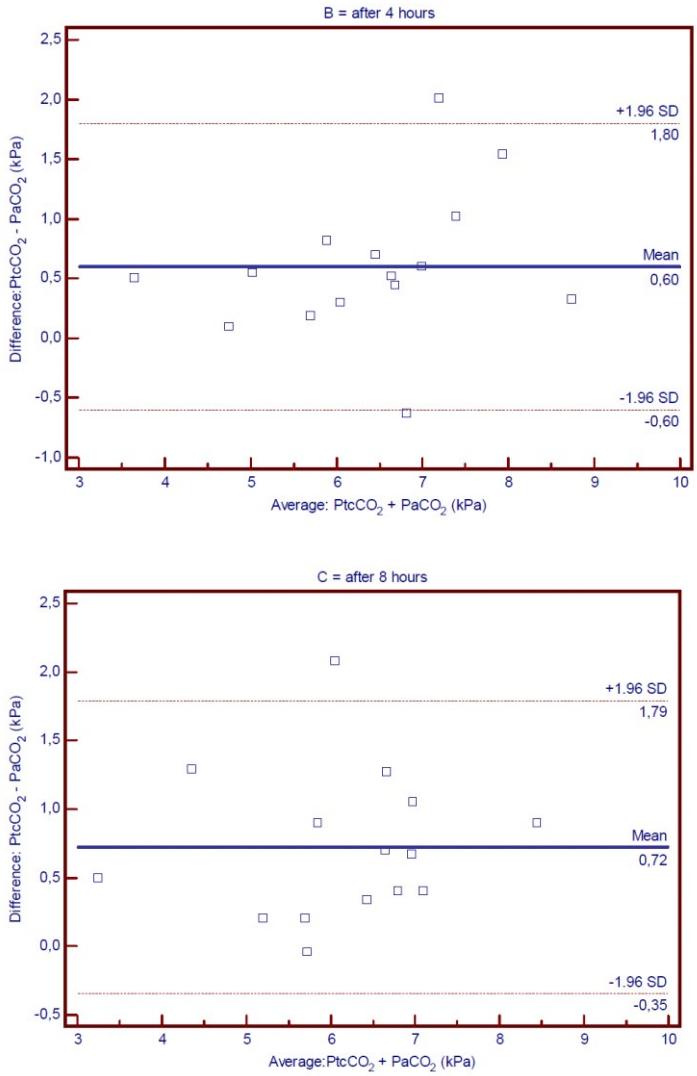
The method of Bland and Altman [17] was used to assess agreement between the arterial blood gas and transcutaneous variables . A maximum bias of 1.0 kPa (7.5 mm Hg) and 95% limits of agreement (LOA) of 1.0 kPa (7.5 mm Hg) between transcutaneous and arterial carbon dioxide pressure measurements were determined as acceptable. A maximum bias of <2 and 95% LOA of 4% were determined as clinically acceptable between arterial oxygen and transcutaneous saturation. To determine whether transcutaneous measurements differ significantly from the arterial values at the same time point we performed a Student's paired t test [10]. Analysis of variance for repeated measurements was used to determine changes from one time point to the next. Data analysis was performed with SPSS version 15 (SPSS Inc., Chicago, Ill., USA) and MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

Eight women and seven men with a mean (SD) age of 58 years were enrolled in the study. The diagnosis was neuromuscular disease in 7 patients, chronic obstructive pulmonary disease in 5 patients and obstructive/central sleep apnoea syndrome in 3 patients. Thirteen patients received chronic ventilatory support and 2 were breathing spontaneously. A total of 75 paired measurements were taken 30 min, 2, 4, 6 and 8 h after attaching the sensor to the earlobe. Correlations are 0.96 after 30 min, 0.90 after 4 h and 0.91 after 8 h. To assess the measurement characteristics of the device, we calculated the bias and LOA as described by Bland and Altman (fig. 1).

Figure 1.



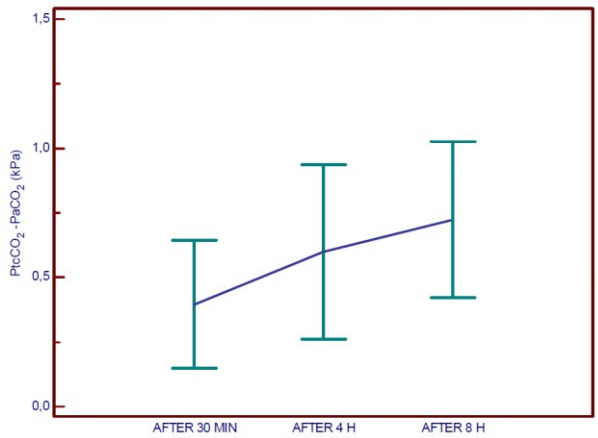


Mean (x-axis) versus difference (y-axis) of transcutaneous and arterial carbon dioxide tension according to Bland and Altman [17] in 15 subjects, 30 min (A), 4 h (B) and 8 h (C) after attaching the sensor to the earlobe.

The mean $PtcCO_2$ was 0.4 kPa (3 mm Hg) higher than the mean $PaCO_2$ after 30 min. This difference increased slightly during the night to a maximum of 0.72 kPa (5.4 mm Hg) after 8 h. The LOA (bias ± 1.96 SD) ranged from –0.48 to 1.27 kPa (3.6 to 9.5 mm Hg) after 30 min, from –0.60 to 1.80 kPa (4.5 to 13.5 mm Hg) after 4 h and from –0.35 to 1.79 kPa (2.6 to 13.4 mm Hg) after 8 h. At all time points the paired difference was highly correlated ($p < 0.004$) with $PaCO_2$. The paired measurements, tested in 15 patients over 8 h, have mean values for

$PtcCO_2$ – $PaCO_2$ after 30 min of 0.39 ± 0.44 kPa (2.9 ± 3.3 mm Hg), after 4 h of 0.59 ± 0.61 kPa (4.4 ± 0.61 mm Hg) and after 8 h of 0.72 ± 0.54 kPa (5.4 ± 4.0 mm Hg) (repeated measures ANOVA, p = 0.253; fig, 2).

Figure 2.

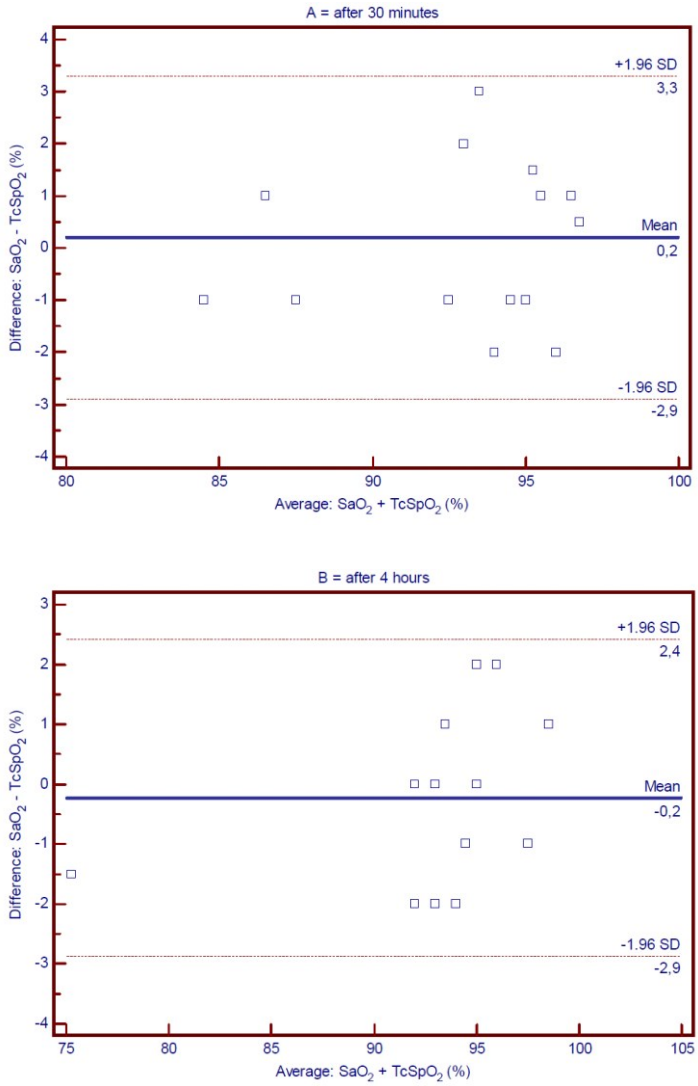


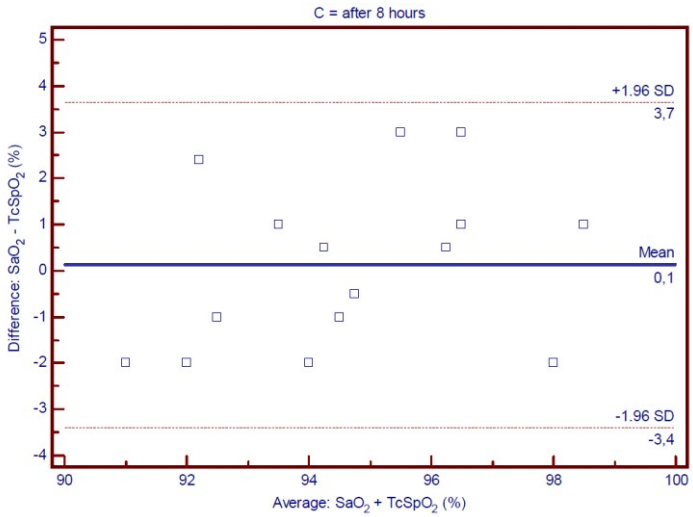
Mean values of $PtcCO_2$ – $PaCO_2$ and SD, in 15 patients. Drift in $PtcCO_2$ over 8 h is not significant (ANOVA).

The observed range of changes in $PaCO_2$ during repeated measurements was –0.7 kPa (5.25 mm Hg) to 1.3 kPa (9.75 mm Hg) and agreement among the changes in $PtcCO_2$ and $PaCO_2$ was close at 0.2 kPa (1.2 mm Hg) [LOA (bias ± 1.96 SD), 1.4 kPa (–10.5 mm Hg) and 1.85 kPa (13.7 mm Hg)], the difference was not significant.

The mean PaO_2 at baseline was 9.4 kPa (70.5 mm Hg), after 4 h 9.9 kPa (74.3 mm Hg) and after 8 h 10.0 kPa (75 mm Hg). Figure 3 shows the agreement between the arterial and transcutaneous oxygen saturation.

Figure 3.


A = after 30 minutes
+1.96 SD
3,3
Mean
0,2
-1.96 SD
-2,9
Difference: SaO2 - TcSpO2 (%)
Average: SaO2 + TcSpO2 (%)
B = after 4 hours
+1.96 SD
2,4
Mean
-0,2
-1.96 SD
-2,9
Difference: SaO2 - TcSpO2 (%)
Average: SaO2 + TcSpO2 (%)



Bias and LOA of arterial and transcutaneous oxygen saturation according to Bland and Altman [17] in 15 subjects, 30 min (a), 4 h (b) and 8 h (c) after attaching the sensor to the earlobe.

Arterial oxygen saturation was between 74 and 99%, while the transcutaneous oxygen saturation was between 76 and 99%. There was only a mean difference (bias) of maximal 0.2% at all time points.

The attachment of the sensor to the earlobe was good, none of the patients showed skin problems due to the sensor or the resulting temperature of 42°C.

Discussion

This study shows that $PtcCO_2$ measurement by the TOSCA® has a clinically acceptable agreement with $PaCO_2$ during 8 h of unsupervized continuous measurement. Earlier studies have also assessed the TOSCA® system in different settings, but none have done this in a non-supervized continual measurement, while asleep, as in our study [3,7-15,18] . All referred studies performed measurements with a reported mean difference (bias) between $PaCO_2$ and $PtcCO_2$ ranging from 0.4 to 1.0 kPa (3 to 7.5 mm Hg). The observed range of changes in $PaCO_2$ during repeated measurements in our study was –0.7 kPa (5.25 mm Hg) to 1.3 kPa (9.75 mm Hg) and agreement among the changes in $PtcCO_2$ and $PaCO_2$ was close at 0.2 kPa (1.2 mm Hg). The difference in CO_2 measurements between transcutaneous and arterial values are small and are not likely to influence the decisions in adjusting the ventilator settings. Measuring the SpO_2 with the TOSCA® sensor revealed a clinically acceptable bias between SaO_2 and SpO_2 of 0.2% difference at all time points. We believe that measuring gas exchange continuously in patients with chronic ventilatory support provides more information about the

changes over night than single arterial measurements during admission on the ICU [19] . Nevertheless, the transcutaneous assessment has some limitations: it lacks information on bicarbonate, pH and arterial oxygen, it is expensive, it needs disposable items for measurements and, finally, it is rather fragile. However, the advantage of not being admitted to the ICU provides a more realistic view of the clinical condition over night. This study suggests that measurement in a high care setting, such as an ICU, might no longer be necessary in many patients, thus saving costs. Currently, we are testing the TOSCA® monitor for registration at home during the initiation phase of HMV, thereby alleviating even more the need for hospitalization and reducing costs. All personnel, whether inside or outside the hospital, require training before working with the TOSCA® transcutaneous monitor.

In summary, we showed that the TOSCA® transcutaneous monitor can be used to replace the arterial sampling with clinically acceptable accuracy in adults with chronic respiratory failure using ventilatory support. Measuring oxygen saturation and carbon dioxide continuously provides more information about changes during the night than single arterial measurements. The sensor was well tolerated in patients during the 8-hour observation period and was not associated with a significant drift of the $PtcCO_2$ signal.

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Chapter 4

Initiation of home mechanical ventilation at home: a randomized controlled trial of efficacy, feasibility and costs

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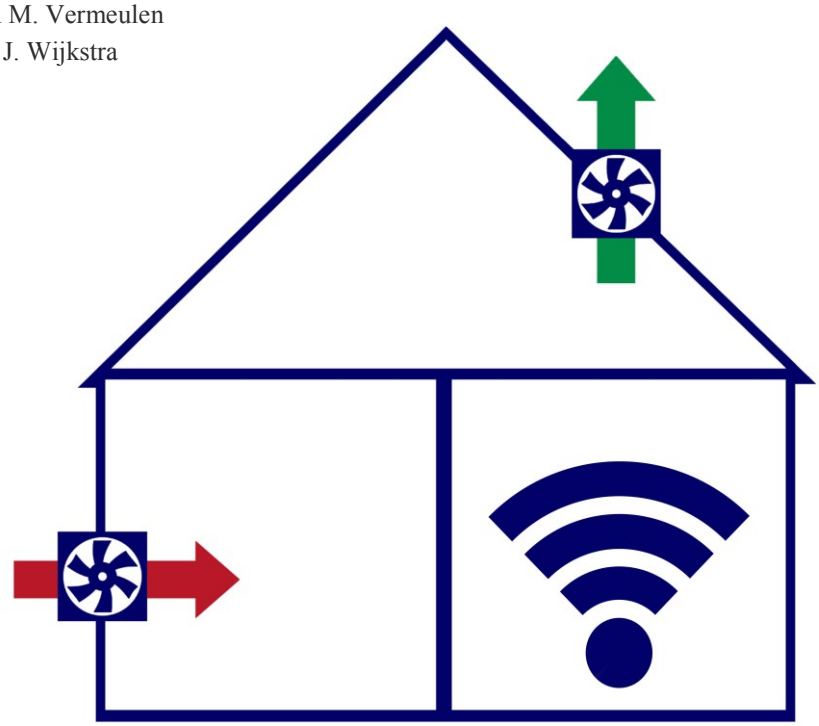


Adapted from:
Respiratory Medicine 2014; 108, 1387-1395

Abstract

Introduction

Home mechanical ventilation (HMV) in the Netherlands is normally initiated in hospital, but this is expensive and often a burden for the patient. In this randomized controlled study we investigated whether initiation of HMV at home in patients with chronic respiratory failure is non-inferior to an in hospital based setting.

Methods

Seventy-seven patients were included, of which 38 patients started HMV at home. All patients were diagnosed with chronic respiratory failure due to a neuromuscular or thoracic cage disease. Primary outcome was the arterial carbon dioxide ($PaCO_2$) while quality of life and costs were secondary outcomes. Telemonitoring was used in the home group to provide therapeutic information, for example; transcutaneous carbon dioxide, oxygen saturation and ventilator information, to the caregivers. Follow-up was six months.

Results

*P*aCO_2, improved by 0.72 (SE ± 0.16) kPa in the hospital group and by 0.91 (±0.20) in the home group, both improvements being significant and the latter clearly not inferior.
There were also significant improvements in quality of life in both groups, again not being inferior with home treatment.

Conclusion

This study is the first to show that initiation of HMV at home in a selective group of patients with chronic respiratory failure is as effective for gas exchange and quality of life as hospital initiation. In addition we found that it is safe, technically feasible and that more than € 3000 per patient can be saved compared to our standard care.

Introduction

Home mechanical ventilation (HMV) in the Netherlands routinely starts in a clinical setting as recommended in the national guideline and typically requires several days, up to a week of hospitalization [1]. Nocturnal arterial blood gas analysis while on HMV complete the initiation period and are performed at the intensive care. It is intuitive that the costs of starting HMV in a hospital setting are substantial higher than at home which is the topic of our study. In addition being admitted to a hospital for patients is not only an emotional burden, it also increases the risk of developing a nosocomial infection [2]. Patients on HMV are mostly severely disabled and it is often, perhaps paradoxically, challenging to provide the same high level of individually tailored care in hospital as compared to home. These are all very important reasons to investigate whether the initiation of HMV cannot be carried out in the home setting.

A problem of the initiation of HMV at home so far has been the lack of professional supervision in the home environment and night time observation during sleep. A probable solution for this problem is the use of telemonitoring to transmit digital data and provide clinical health care outside the hospital [3] and [4]. The data in patients with HMV comprises of ventilator settings and physiological data, for example carbon dioxide and oxygen saturation levels. It has been shown that telemonitoring can be cost-effective and in certain settings is able to transfer the burden of care from health-care professionals to family and home-care personnel [5]. In the latter study patients with chronic obstructive pulmonary disease (COPD) on oxygen or HMV were monitored by tele-assistance which reduced both hospitalizations and urgent calls compared to the control group that received standard care.

As we do not know if the initiation of HMV at home is effective, technically feasible and cost-effective we set up a randomized controlled trail.

Our hypothesis was that initiation of HMV at home, by using telemonitoring, in a selective group of patients with chronic respiratory failure due to neuromuscular disease (NMD) or thoracic cage disorder is not inferior compared to initiation in a hospital. The primary outcome measure was the arterial carbon dioxide ($PaCO_2$) while quality of life and costs were secondary outcome measurements.

Methods

Subjects

The study design was single-centre, prospective, randomized and controlled. Patients diagnosed with chronic respiratory failure due to a NMD or thoracic cage disorder being

referred to our outpatient clinic were screened for participation in this study. Chronic respiratory failure was defined as daytime $PaCO_2$ > 6.0 kPa (> 45 mmHg) [6] and [7] with complaints of respiratory failure (pulmonary infections, headache, daytime sleepiness, concentration problems) as stated in our national guideline [1]. Patients with orthopnoea due to diaphragm paralysis and daytime normocapnia were also included. Patients younger than 18 years, those who needed invasive ventilation and the ones that lived in a nursing home were excluded. We excluded patients with strictly COPD as HMV is not a standard therapy in the Netherlands in those patients. Patients not naïve to a mask, for example failure after CPAP therapy and patients with an acute episode of respiratory failure were also excluded. The study was approved by the Medical Ethics Committee of the University of Groningen, University Medical Centre of Groningen and written informed consent was obtained from all patients. The trial was registered with the Netherlands Trial Registry (NTR number 1476).

Randomization and intervention

Patients started HMV at home or in the hospital in random order. Stratification was done for patients with Amyotrophic Lateral Sclerosis (ALS) to prevent a possible imbalance between the two groups. Randomization was done by an independent statistician using a stratified block randomization with a block size of 6.

Measurements

Daytime arterial blood gasses were taken from the radial artery, in sitting position and without oxygen supplementation or HMV at baseline and 6 months after the initiation of HMV at the outpatient clinic.

Patients completed the following questionnaires: Severe Respiratory Insufficiency (SRI) [8], Maugeri Respiratory Failure (MRF-28) [9], Hospital Anxiety and Depression Scale (HADS) [10] and the Short-Form Health Survey (SF-36) [11].The SRI contains seven domains; respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being and social functioning. The MRF contains three domains; daily activity, cognitive function and invalidity. The HADS contains the anxiety and depression domain. The SF-36 contains eight domains; physical functioning; role physical; bodily pain; general health; vitality; social functioning; role emotional and mental health.

Forced vital capacity was measured by spirometry (Masterscreen® Viasys, Bodystat Ltd, Isle of Man, UK.).

Carbon dioxide and oxygen saturation were assessed through the skin of the earlobe, by TOSCA® (Linde Medical Sensors AG. Basel. Switzerland) [12].

A standard procedure describing the technical setup of HMV was used both at home and in the hospital. All patients started with the Elisée 150® ventilator (ResMed Paris, Fr.). The choice of the interface could be a nasal, full-face, mouth or total-face mask. The ventilator in the pressure

mode was set up at the start with an inspiratory pressure of 10 cm H_2O; a positive end expiratory pressure (PEEP) of 4 cm H_2O; a target volume of 8–10 ml/kg and a ventilatory rate close to the patients breathing frequency. The set up in the volume mode started at a volume of 8–10 ml/kg; a PEEP of 4 cm H_2O and a ventilatory rate close to the patients breathing frequency. The standard procedure described which actions should be taken to change the ventilator settings during the initiation of HMV. For example, if the patient needed more air, the inspiratory pressure was increased and if the patient snored during the PEEP was increased. During the initiation of HMV adjustments to the ventilator and or interface were done to improve the blood gasses and the patients comfort resulting in a good night sleep.

Initiation of home mechanical ventilation in the hospital

Standard care during the initiation of HMV in our hospital entails admission on a regular respiratory ward with specifically trained personnel. The first day of admission the patient started HMV with the intention to get used to the interface and to adjust to the ventilator settings. Patients were instructed to use the ventilator as long as possible during the first night. They were allowed to stop the HMV during the night and if applicable start again early in the morning for another session. Every day the necessary actions including, adjusting ventilator settings or interface were performed. The patient had to sleep at least 6 h with the ventilator, before he was transferred to the intensive care unit (ICU) to assess arterial blood gasses, through a radialis catheter, during the night while using the HMV. The latter being the standard routine in the Netherlands. If normalization of carbon dioxide and oxygen saturation levels while on the ventilator were reached, the patient was discharged. The ventilator was installed at home by a nurse of the department of HMV. After two months the patient was admitted again to the ICU for nocturnal arterial blood gas assessment while on HMV. The patient had to bring their own home ventilator to the hospital.

Follow-up was six months after starting HMV at the outpatient clinic to assess an arterial blood gas analysis and lung function.

Initiation of HMV at home started during the first visit at the patient's home by the nurse practitioner (NP). The ventilator, humidifier and transcutaneous monitor were installed in the patient's bedroom (Fig. 1).

Figure 1. Setup of the telemonitoring equipment at home.

Ventilator Elisée 150®, humidifier Fisher and Paykel HC 150®, transcutaneous monitor TOSCA®, laptop with mobile connection.

This installation also included the laptop, mobile connection and the software program that was used to send digital data of the devices to the hospital. The first time the patient was ventilated the NP was present. After instruction was given to the patient and if necessary to the caregivers they practiced the HMV themselves at daytime. If in the first night, when trying to sleep with the HMV, the patient woke up and could not continue because of discomfort they were allowed to stop. The following days and nights they tried to extend the number of hours on HMV. Patients were instructed to call the department of HMV 24/7 if problems occurred. If sputum mobilization was a problem patients were instructed to use air stacking and one ventilator mode was adjusted for mouthpiece ventilation. Every day the ventilator information (e.g. volume, frequency, pressure levels, hours ventilator was used) was sent to the hospital and evaluated by the NP. The NP informed the patient about the results over the telephone and if necessary the ventilator settings were adjusted by the patient or the care giver. Changing the ventilator settings while on the phone with the NP is part of the instruction at the start of HMV. The transcutaneous monitor was attached the moment the patient could sleep for six hours while being on HMV. The next day the measurements of the transcutaneous monitor and the

ventilator were evaluated, by using telemonitoring. When the results showed a normalization of the carbon dioxide and oxygen saturation, the initiation period was ended during a house call by the NP. The transcutaneous monitor and the telemonitoring equipment were returned to the hospital. Two months after the initiation of HMV, transcutaneous monitoring at home was performed again.
Follow-up was six months after starting HMV at the outpatient clinic to assess an arterial blood gas analysis and lung function.

Telemonitoring

Every morning during the initiation period of HMV at home, the data of the ventilator and if applicable of the transcutaneous monitor was sent to the hospital. The data comprized of ventilator settings, respiratory rate and carbon dioxide and oxygen saturation levels. The NP received the anonymized digital data by email and phoned with the patient to evaluate the results. A laptop was used to transfer the information collected by the ventilator and transcutaneous monitor to the hospital. A software program especially developed for this study started the data collection of the ventilator and transcutaneous monitor automatically.

Cost analysis

Units of health care consumption that were registered included admission days to the general ward and ICU, time spent by the nurse practitioner (including house calls) and travelling expenses. Volumes of health care consumption were multiplied with their cost prices according to the Dutch guideline for cost studies [13]. The 2012 price level was used. Costs are displayed in Euro's (€). The time horizon of the cost study was equal to that of the clinical study and was 6 months. Mean total costs per patient were calculated for both interventions separately. Confidence intervals (95%CI's) were computed based on bootstrap re-sampling with 5000 replications of the trial dataset.

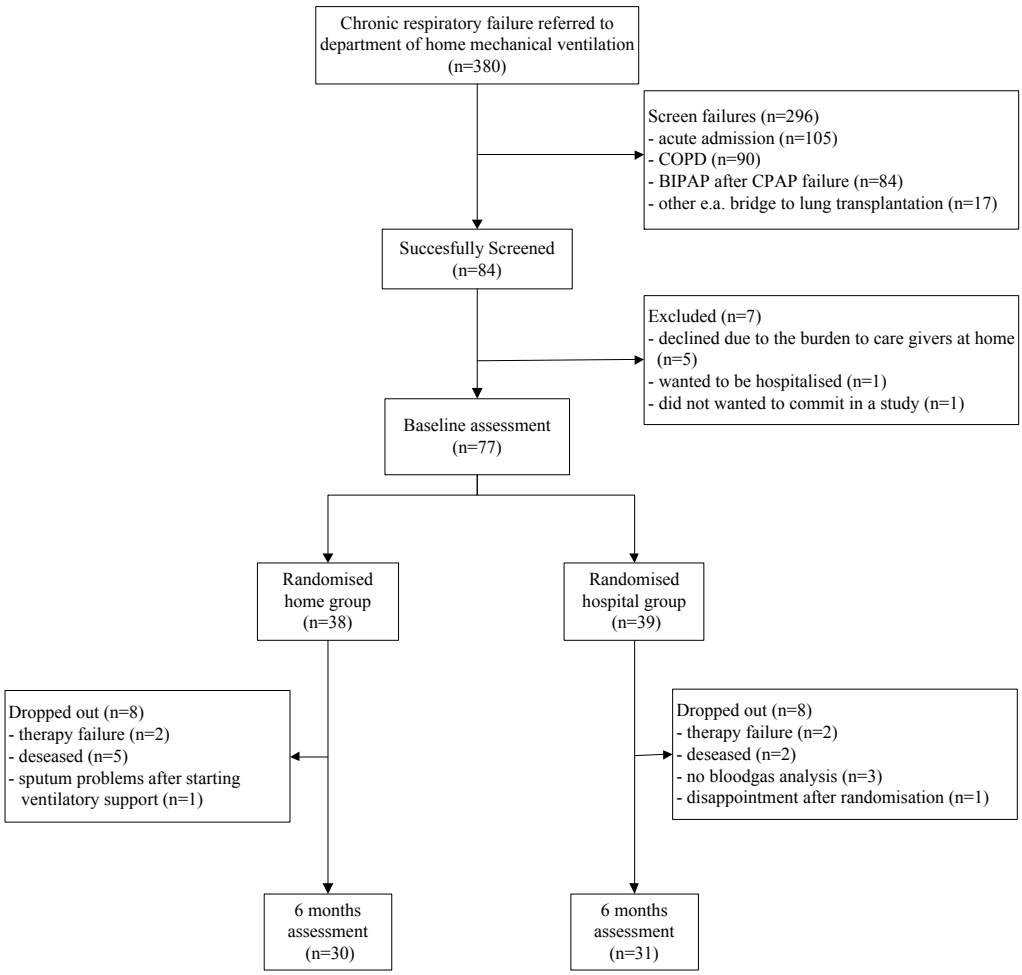
Statistical analysis

The primary outcome analysis was $PaCO_2$ which was based on intention-to-treat (ITT) analysis. The power analysis was based on a non-inferiority test of the difference of two means. With an alpha of 0.05, a beta of 0.2, a standard deviation off 0.71 and a maximum difference in $PaCO_2$ of 0.5 kPa, it was necessary to have two groups off 26 patients. A paired-sample T-test was performed to determine the difference within groups and an independent-sample T-test for the difference (Δ) between groups. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics 20 (IBM, New York, USA).

Results

380 patients started non-invasive HMV in the University Medical Centre of Groningen (UMCG) during the inclusion period which lasted from 2008 till 2012 (Fig. 2).

Figure 2. Flow diagram



Home group: initiation of home mechanical ventilation at home. Hospital group: initiation of home mechanical ventilation in the hospital. COPD: chronic obstructive pulmonary disease. BIPAP: bi-level positive airway pressure. CPAP: continuous positive airway pressure.

Of the 84 patients that were eligible, 77 were randomized (Table 1).

Table 1. Baseline characteristics.

	Home group (n=38)	Hospital group (n=39)
Male	20	25
Age in years	59.9 ± 12.6	56.9 ± 13.9
Neuromuscular disease	33	35
Thoracic cage disorder	5	4
Body mass Index kg-m^2	27 ± 6.3	27 ± 6.8
Blood gas analysis room air		
Ph	7.40 ± 0.3	7.40 ± 0.3
$PaCO_2$ kPa	6.6 ± 0.9	6.6 ± 1.1
PaO_2 kPa	10.0 ± 1.7	9.5 ± 1.3
SaO_2 %	95 ± 2.9	94 ± 2.7
HCO_3 mmol/l	30.2 ± 3.8	30.4 ± 3.8
VC % predicted	50.3 ± 20.9	51.6 ± 18.1
FEV_1 / VC	79.3 ± 12.2	81.2 ± 15.7
Pack years	14.3 ± 11.2	29.5 ± 17.8
Current smokers	2	3
Wheelchair-bound	16	12

Data are presented as n or mean ± SD.
kPa: kilopascal. Ph: acidity level. $PaCO_2$: partial pressure of arterial carbon dioxide. PaO_2: partial pressure of arterial oxygen. SaO_2: arterial oxygen saturation. HCO_3: bicarbonate. VC: vital capacity. FEV_1: forced expiratory volume in one second.

Eight in each group withdrew during follow-up (Table 2).

Table 2. Drop-out with reasons.

	Diagnosis	Reason
Home group		
1	Morbus Steinert	Developed lung cancer
2	Amyotrophic lateral sclerosis	Death due to progression disease
3	Amyotrophic lateral sclerosis	Euthanasia
4	Amyotrophic lateral sclerosis	Palliative sedation
5	Amyotrophic lateral sclerosis	Palliative sedation
6	Amyotrophic lateral sclerosis	Euthanasia
7	Primary lateral sclerosis	Not compliant to home mechanical ventilation
8	Diaphragm paralysis	Paralysis recovered
Hospital group		
1	Amyotrophic lateral sclerosis	Disappointment after randomization
2	Diaphragm paralysis	Not compliant to home mechanical ventilation
3	Von Recklinghausen type 1	Not compliant to home mechanical ventilation
4	Amyotrophic lateral sclerosis	Arterial blood gas analysis not possible
5	Amyotrophic lateral sclerosis	Death due to progression disease
6	Amyotrophic lateral sclerosis	Palliative sedation
7	Amyotrophic lateral sclerosis	Arterial blood gas analysis not possible
8	Amyotrophic lateral sclerosis	Arterial blood gas analysis not possible

The largest group in this study was diagnosed with ALS (4 with bulbar involvement); 10 patients in the hospital group had diaphragm paralysis and 4 in the home group. Two patients crossed from intervention, one in the hospital group and the other in the home group. They remained in the initial group for all ITT analysis. Both analysis per protocol and ITT did not resulted in different outcomes. We also evaluated the variety in diagnoses and did not find a significant difference between both groups.

One patient with limb girdle dystrophy in the home group and 1 patient with ALS in the hospital group used HMV when their blood gasses were assessed during 6 months follow-up due to the progression of their illness.

In the home group 5 patients died versus 2 in the hospital group. In no case was this due to technical problems in the home settings. Patients died varying from one week up to almost 6 months after starting HMV, all experiencing a non-acute progression of their disease (ALS).

Twenty-five patients in the home group and 28 patients in the hospital group were not able to perform physical activities regarding the maintenance of HMV. The care givers were instructed

during the initiation of HMV at home while this was done after being discharged in the hospital group.

Blood gas analysis and ventilator settings

Daytime $PaCO_2$, the primary endpoint, improved by 0.72 (SE ± 0.16) kPa in the hospital group and by 0.91 (± 0.20) in the home group being not significantly different between both groups (Table 3).

Table 3. Changes in daytime arterial blood gasses and lung function pre home mechanical ventilation to 6 months after the start.

	Home group (n=30)			Hospital group (n=31)			Between groups
	Baseline	Follow-up	P-Value*	Baseline	Follow-up	P-Value*	P-value¶
Ph	7.40 ± 0.3	7.40 ± 0.3	0.261	7.40 ± 0.3	7.40 ± 0.3	0.913	0.423
$PaCO_2$ (kPa)	6.6 ± 0.9	5.7 ± 0.8	**0.000**	6.6 ± 1.1	5.9 ± 0.8	**0.000**	0.631
PaO_2 (kPa)	10.0 ±1.7	11.3 ± 2.2	**0.002**	9.5 ± 1.3	10.3 ± 1.7	**0.015**	0.579
SaO_2 %	95 ± 2.9	96 ± 1.9	**0.020**	94 ± 2.7	95 ± 3.6	0.348	0.598
HCO_3 (mmol/l)	30.2 ± 3.8	26.6 ± 3.1	**0.000**	30.4 ± 3.8	26.9 ± 2.5	**0.000**	0.996
aBE	4.9 ± 2.6	2.6 ± 1.7	**0.000**	4.8 ± 2.8	2.2 ± 1.8	**0.000**	0.283
VC (% pred)	51.6 ± 22.8	53.4 ± 21.8	0.528	52.4 ± 18.5	49.8 ± 19.0	0.301	0.428

Data are presented as n or mean ± SD.
kPa: kilopascal. Ph: acidity level. $PaCO_2$: partial pressure of arterial carbon dioxide. PaO_2: partial pressure of arterial oxygen. SaO_2: arterial oxygen saturation. HCO_3: bicarbonate. VC: vital capacity. Follow-up: six months after the initiation of home mechanical ventilation.
Bold: $p < 0.05$ significant change.
P-value* refers to paired t test analysis form starting ventilatory support to six months follow-up within each group.
P-value¶ for difference in change from baseline between groups.

Nocturnal transcutaneous registration showed an improvement in both groups, both after initiation and after two months (Table 4).

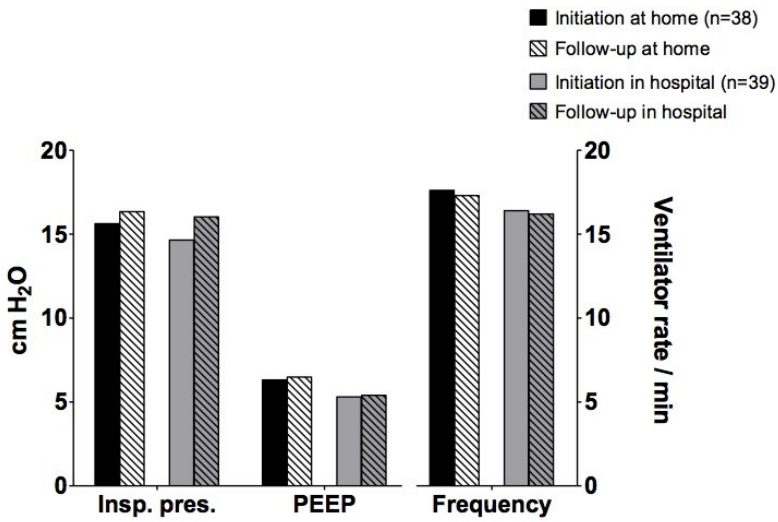
Table 4. Changes in nocturnal transcutaneous carbon dioxide and oxygen saturation.

	Home group (n=30)			Hospital group (n=31)		
	Baseline	After initiating HMV	2 months follow-up	Baseline	After initiating HMV	2 months follow-up
$tcpCO_2$ (kPa)	7.6 ± 1.0	6.5 ± 0.9	5.8 ± 0.7	7.4 ± 1.3	6.4 ± 0.8	5.7 ± 0.7
Maximal $tcpCO_2$ (kPa)	8.7 ± 1.4	7.3 ± 0.9	6.7 ± 0.8	8.4 ± 1.8	7.3 ± 0.9	6.6 ± 0.2
Oxygen saturation (%)	91.3 ± 5.1	95.2 ± 1.8	96.2 ± 1.8	91.8 ± 4.9	95.7 ± 1.7	95.9 ± 1.7
Lowest oxygen saturation (%)	74.6 ± 15.2	86.6 ± 8.2	84.7 ± 12.8	74.4 ± 14.6	84.1 ± 9.2	85.7 ± 7.2

Data are presented mean ± SD.
$tcpCO_2$: transcutaneous carbon dioxide. kPa: kilo pascal

Both groups started with the same ventilator settings and only minor adjustments were needed during the follow-up of six months (Fig. 3).

Figure 3. Ventilator settings.



Ventilator settings from initiation to six months follow-up. Insp. pres: inspiratory pressure in cm H2O above peep. PEEP: positive end expiratory pressure in cm H2O. Frequency: ventilator frequency. Initiation: after the initiation of home mechanical ventilation. Follow-up: 6 months follow-up after starting home mechanical ventilation.

Three patients were ventilated in the volume mode and the other 74 in the pressure controlled mode. In the home group a mean of 11 (±1.86) days was needed to initiate HMV and in the hospital group 8 (±0.54) days. Follow-up after 6 months showed that patients at home slept a mean of 10.0 (±0.83) hours with HMV and the hospital group 8.5 (±0.67) hours.

Health related quality of life

The hospital and home group improved significantly on two of seven SRI subscales. The improvements in SRI score form baseline to six months follow-up were not inferior (or significantly better) in the home group compared to the hospital group.

The MRF-28 showed a significant improvement in the hospital group on the total score but not in the home group, however not being significantly different between both groups. The other MRF-28 domain scores were both within and between groups not significantly different. The HADS showed no significant changes both within and between groups. The SF-36 showed a significant improvement in the domain vitality in both groups. The other SF-36 domains showed no significant changes between groups (Table 5).

Table 5. Changes in health related quality of life measurements pre home mechanical ventilation to 6 months after the start.

	Home group (n=30)			Hospital group (n=35)			Between groups
	Baseline	Follow-up	P-Value*	Baseline	Follow-up	P-Value*	P-value¶
SRI							
RC	47.6 ± 19.5	55.5 ± 17.3	**0.023**	48.6 ± 18.5	51.9 ± 17.6	0.114	0.462
PF	28.8 ± 21.4	31.9 ± 21.5	0.994	36.6 ± 20.5	32.9 ± 20.5	0.452	0.585
AS	55.1 ± 18.6	69.6 ± 18.0	**0.000**	48.5 ± 19.1	60.9 ± 16.7	**0.000**	0.904
SR	68.5± 12.3	69.5 ± 12.7	0.723	71.2 ± 12.8	66.9 ± 11.8	0.204	0.247
AX	55.0 ± 21.1	57.8 ± 24.2	0.474	54.7 ± 16.8	60.9 ± 16.7	0.159	0.628
WB	57.1 ± 19.8	57.3 ± 24.0	1.000	60.3 ± 15.7	59.7 ± 18.3	0.946	0.963
SF	52.7 ± 19.1	51.9 ± 22.3	0.298	57.2 ± 17.5	55.1 ± 18.5	0.733	0.603
SS	52.1 ± 14.4	56.2 ± 16.4	0.153	53.9 ± 12.3	55.4 ± 12.0	0.248	0.762
MRF-28							
Daily activities	58.1 ± 27.9	59.7 ± 27.6	0.741	60.3 ± 29.0	53.2 ± 28.1	0.182	0.706
Cognition	35.0 ± 32.6	29.4 ± 33.5	0.372	37.1 ± 35.4	30.0 ± 34.7	0.143	0.836
Invalidity	53.3 ± 38.5	61.3 ± 37.1	0.241	57.1 ± 34.7	57.1 ± 34.7	1.000	0.333
Total score	52.1 ± 21.1	49.2 ± 23.1	0.466	58.2 ± 19.7	45.2 ± 20.9	**0.000**	**0.038**
HADS							
Depression	6.6 ± 4.2	6.0 ± 4.5	0.319	7.1 ± 3.5	6.4 ± 4.2	0.139	0.985
Anxiety	6.4 ± 4.7	6.1 ± 4.9	0.193	6.8 ± 3.8	6.1 ± 3.4	0.195	0.589
Total score	13.0 ± 8.0	12.1 ± 8.7	0.660	13.9 ± 6.8	12.5 ± 7.1	0.175	0.760
SF-36							
PF	13.2 ± 18.5	15.6 ±19.1	0.832	17.1 ± 22.1	18.8 ± 23.6	0.784	0.983
RP	15.7 ± 33.6	25.0 ±35.9	0.565	13.1 ± 24.4	25.7 ± 35.0	**0.013**	0.337
BP	66.8 ± 30.7	66.1 ± 29.6	0.853	64.2 ± 29.2	60.5 ± 24.5	0.612	0.863
GH	30.7 ± 24.8	35.2 ± 27.2	0.805	30.2 ± 17.3	36.0 ± 19.6	0.058	0.205
VT	39.0 ± 21.4	52.1 ± 22.6	**0.004**	36.5 ± 18.9	45.2 ± 18.9	**0.004**	0.967
SF	52.6 ± 32.9	58.7 ± 32.8	0.881	55.0 ± 21.7	60.3 ± 27.3	0.338	0.602
RE	54.3 ± 52.8	57.4 ± 47.0	0.508	48.2 ± 46.3	57.1 ± 45.4	0.209	0.864
MH	66.3 ± 21.8	72.2 ± 22.0	**0.040**	64.7 ± 17.5	69.7 ± 17.0	0.055	0.993

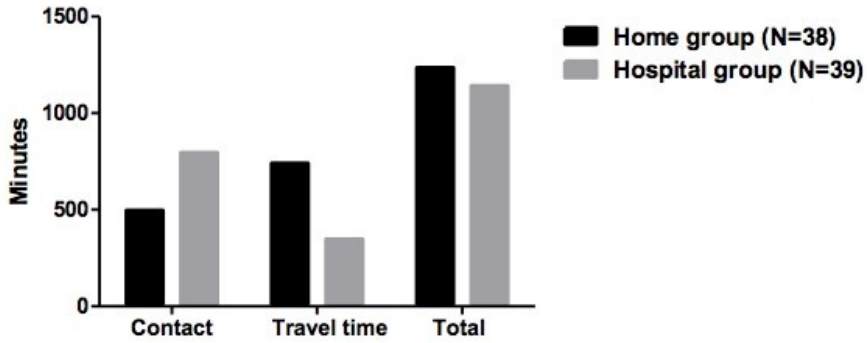
Data are presented as n or mean ± SD
SRI: Severe Respiratory Insufficiency (0 = worst possible health 100 = best possible health) respiratory complaints (RC), physical functioning (PF), attendant symptoms and sleep (AS), social relationship (SR), anxiety (AX), psychological well-being (WB), social functioning (SF), summary score (SS)
MRF-28: Maugeri Respiratory Failure (0 = best possible health 100 = worst possible health)
HADS: Hospital Anxiety Depression Scale (total score: 0 = best possible health 42 is worst possible health; separate score 0-21)
SF-36: Short-Form Health Status Survey (0 = worst possible health 100 = best possible health) PF = physical functioning, RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health.

Bold: p <0.05 significant change.
P-value* refers to paired t test analysis form starting ventilatory support to six months follow-up within each group.
P-value¶ for difference in change Δ from baseline between groups.

Costs

Due to the travel time in the home group the total invested time by NP per patient was 91 min longer compared to the hospital group. In contrast the contact time per patient in the hospital group was higher (Fig. 4). The NP visited the patient the first day and if necessary the following days. This was not specified in the standard procedure and resulted in a mean of 3 visited during the initiation period of HMV.

Figure 1. Time spent during initiation of home mechanical ventilation and 6 months follow-up.



Contact: direct contact between the patient and the care giver of the department of home mechanical ventilation from initiation to 6 months follow-up. Travel time: driving time between hospital and patient during house calls. Total: is all time added up.

Total mean costs per patient amounted to € 726 per patient in the home group and to € 3913 in the hospital group (difference - € 3187; 95% CI - € 3643 to - € 2694). Mean costs in the hospital group amounted to € 3618 for admission to the ICU and the ward, €198 for contact with the NP and € 97 for travelling expenses. Mean costs in the home group included € 192 of travelling expenses, € 266 of house calls and consult by telephone by the nurse practitioner, and € 268 for hospital admissions. As the other costs; masks, ventilator, disposables supply and transcutaneous measurement were similar in both groups this was not accounted for.

Telemonitoring

Since the procedure of initiation of HMV at a distance, i.e. at home, is new and the software program for telemonitoring was specifically developed for this study, patients were instructed to contact the 24/7 call service of the HMV department if necessary. The use of telemonitoring

did not result in problems or calls during the night. Adjusting ventilator settings, while interacting with the patient or caregivers, went well after good instructions during the initiation process.
Technical problems did occur initially in 11 out of the 38 patients who started HMV at home. In 3 patients the wireless connection was not successful because of insufficient mobile connection facilities as our part of the country is not very densely populated. Another reason was that patients with ALS sometimes live in an iron surfaced mobile unit, with bedroom and washroom facilities on the ground floor. The iron surface disturbs the mobile connection. In these 11 cases the evaluation of the patients' condition was done on individual clinical parameters; sleeping time with HMV, sleep quality and improvement of quality of life during the day.

Discussion

This is the first study showing that initiation of home mechanical ventilation at home, in a selective group of patients with a stable respiratory problem, resulted in improvements in blood gasses and quality of life being not inferior to in hospital initiation. In addition it showed that the start of HMV at home, by using telemonitoring, was safe, feasible and cheaper.
Publications concerning the initiation of HMV outside the hospital by using telemonitoring are scarce. One study showed a reduction in health care utilization in patients with ALS after using home telemonitoring [14]. Initiation of HMV was done in the hospital and the follow-up was carried out at home by using telemonitoring. They used a fixed telephone line with limited speed of data transferral. In our study we started HMV at home and we used a mobile connection allowing us to move the equipment from one patient to the other without technical workout delays. Another study showed that telemonitoring can be more effective in patients who are more compliant to the therapy [15]. The installation of the telemonitoring system at the patient's home in our study was self-supporting meaning that the data transfer was not dependent on the technical skills or actions to be taken by the patient or compliance to therapy.
A third study compared the initiation of HMV between inpatient and outpatient titration but did not use telemonitoring [16]. The improvement of blood gasses was equivalent between the two groups which is comparable to our study. However patients included in our study had a mean $P\mathrm{aCO_2}$ of 6.6 kPa while in the study of Chatwin patients had near normal daytime $P\mathrm{aCO_2}$.
Our data provides a good example in the field of implementation of telemonitoring while not all studies have been successful so far. We believe that the results of this study contribute to the fact that the use of modern technologies in patients with a chronic disease can lower the burden to the health care system.
Earlier studies showed an improvement in blood gasses after the initiation of HMV [17] and [18]. We found a comparable improvement in blood gasses in both groups indicating that the

initiation of HMV can be performed effectively at home in a selective group of patients with chronic respiratory failure due to a neuromuscular disease of thoracic cage disorder. Nevertheless it is obvious that a thorough scan of the home environment must be performed before starting HMV.

This study also showed that it is possible to initiate HMV at home in patients with an age varying from 19 to 80 years of age. The youngest and the oldest started HMV at home and we did not notice any age related problems. In some cases the absence of a partner or family member resulted in recruiting home care professionals to support the patient during the first steps of HMV at home. In the home group patients started HMV one week after being included and in the hospital group this was 3 weeks. This delay in the hospital group was due to limited number of beds in the hospital.

As in our centre the initiation of HMV is done in a hospital based setting and therefore expensive, the present study was performed to search for an alternative. The medical ethics committee agreed to initiate HMV outside the hospital directly instead of starting in an outpatient clinic or on a ward without ICU admission first. This was done to save time and to facilitate patients to stay at home. Initiating HMV at home was not only effective and safe, it was also cost-effective. This study showed a mean reduction of € 3187 per patient when HMV started at home. Mobile data communication costs were negligible and variable and therefore not included in the total costs analysis. Since we initiate HMV in the Netherlands in approximately 600 patients per year [19], full implementation nationwide would save over € 1.8 million annually. Despite this enormous cost reduction we should stress the point that the inpatient initiation is very expensive being primarily due to the ICU admission. When the initiation is done on a non-ICU ward the benefit in costs would be lower compared to our situation.

Despite these positive results this study has some limitations.

Above all, there was a large group of patients with chronic respiratory failure that did not participate in this study for various reasons (Fig. 1). We excluded all patients with COPD as providing HMV to this group is still not current practice in our country. A recent meta-analysis showed that HMV in stable patients with COPD did not improve gas-exchange, lung function or QOL [20]. In this study only 2 patients with OHS were enrolled which is remarkable considering the growth of patients with OHS that start HMV [21]. The reason was that 27 patients with OHS had to start with HMV in hospital immediately due to an acute respiratory failure.

Secondly, the effect of HMV with regard to quality of life (QOL) in our total group compared to previous studies seems to be less positive. Probably this is due to the large number of ALS patients included in our study, which was over the 35%. Although Bourke concluded that HMV in ALS does improve QOL, this was based on the increased duration of time (compared to control group) that the QOL was maintained above 75% of their baseline value [22]. As we assessed absolute values of QOL it is difficult to compare both studies. If we excluded the ALS

group we did find a significant improvement in several domains being comparable with the previous studies.
Another limitation of this study was that the initiation of HMV was done by just one NP in the home group. As we cannot conclude, based on this single study, that it can be duplicated in all other situations, we recommend an additional study were the implementation of this concept on a broader scale i.e. other regions, settings and with more people involved should be examined. Improvements in the technical and digital opportunities, during the last couple of years, will facilitate the development of future telemonitoring studies. Especially the use of polysomnography and microchip cards with detailed ventilator information, can be of great importance in future studies to better evaluate the patient-ventilator interaction.

Conclusion

In summary we showed that initiation of HMV at home in a selective group of patients with chronic respiratory failure due to neuromuscular disease or thoracic cage disorder is effective for gas exchange and quality of life and is not less effective than initiation in the hospital. In addition we found that it is safe and that more than € 3000 per patient can be saved. From a patients' perspective it is an ideal treatment as they do not have to be admitted to the hospital and their highly individualized care can be maintained during the initiation of HMV.

Statement of interest

This study was financially supported by the Health Care Insurance Board in the Netherlands, the University Medical Centre Groningen, Vivisol Area UK & Benelux and ResMed.

Acknowledgments

We are very grateful to all the patients, their family members and the homecare professionals who kindly agreed to participate in this study and to everyone who worked on this project. We would also like to thank the members of the Data Safety Monitoring Board; Prof. Dr. J.G. Zijlstra, Prof. Dr. E.R. van den Heuvel (University Medical Centre Groningen) and Mw. Drs. A.F. Meinesz for their contribution.

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Chapter 5

Is chronic ventilatory support really effective in patients with amyotrophic lateral sclerosis?

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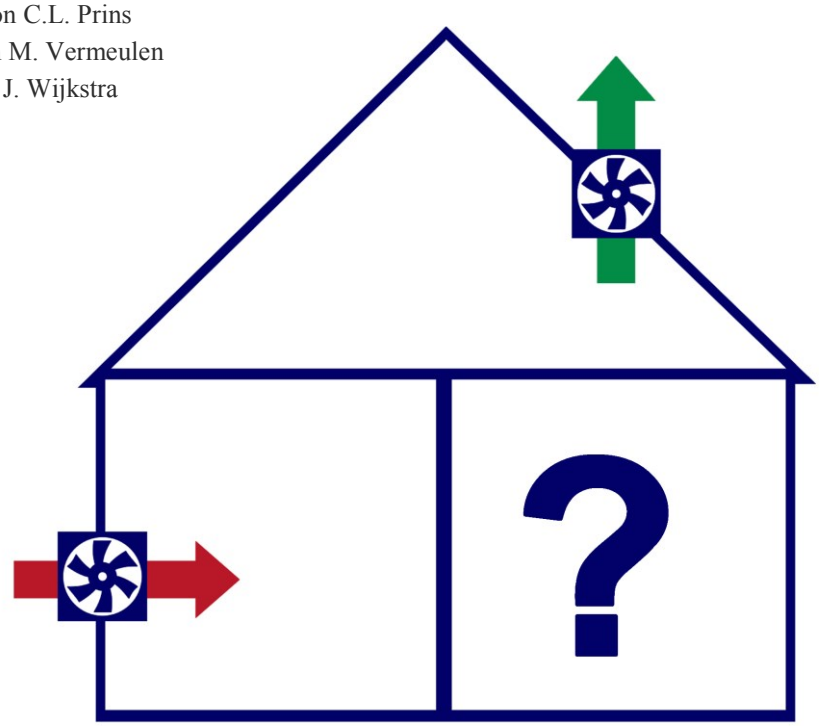


Adapted from:
Journal of Neurology 2016; 263(12), 2456-2461

Abstract

Introduction

Most patients with amyotrophic lateral sclerosis (ALS) develop respiratory insufficiency in the advanced stage of their disease. Non-invasive ventilation (NIV) is commonly regarded to be a treatment that is effective in reducing these complaints.

Objectives

To assess whether the effect of NIV on gas exchange and quality of life (QOL) is different in patients with ALS versus without ALS.
Methods: A post-hoc analyses was done with data from a previously published trial, in which all patients were instituted on NIV. Arterial blood gasses were assessed next to QOL by generic as well as disease specific questionnaires.

Results

77 Patients started NIV; 30 with ALS and 47 without. Both groups showed significant improvements in blood gasses after 2 and 6 months. Compared to the non-ALS group, the ALS group had significantly worse scores after 6 months in MRF-28, SRI, HADS and SF-36 than the non-ALS group.

Conclusion

This study shows that NIV improves gas exchange, both in patients with and without ALS. QOL improves markedly more in patients without ALS than in those with ALS, in whom only some domains improve. Our observation of little or no effect in ALS patients warrants a large study limited to ALS patients only.

Introduction

Most patients with amyotrophic lateral sclerosis (ALS) develop complaints of dyspnoea, fatigue, unrefreshing sleep and morning headache in the advanced stage of their disease due to respiratory insufficiency. Chronic ventilatory support is commonly regarded to be a treatment that is effective in reducing these complaints.

Several studies presented data regarding the effects of chronic ventilatory support on quality of life (QOL) in patients with ALS. Some were positive, while others produced more reservations regarding chronic ventilatory support in these patients. In 2001, in a prospective study, QOL following non-invasive ventilation (NIV) was assessed with two questionnaires, the ALS functional rating scale-respiratory version (ALSFRS-R) and the Short Form 36 (SF-36) [1]. Early intervention of NIV resulted in an improved vitality compared to standard care in this study. In 2003, Bourke et al. presented the results of a cohort study on indications and effect of NIV on QOL in ALS patients. They used the SF-36 to assess QOL in 10 participants using NIV. In this study, the use of NIV was associated with an improved QOL and survival [2]. Finally, a third cohort study on the effects of NIV on ALS patients showed that one month after starting chronic ventilatory support, both blood gasses and QOL improved [3]. In 2006, Bourke assessed the effect of NIV, QOL and survival in participants with ALS in a randomized controlled trial [4]. Their conclusion was that NIV use in patients without bulbar dysfunction was associated with an improved QOL in some domains and a longer maintained QOL above 75 % of the pre-randomization QOL assessed by SF-36. Despite the results mentioned above, Piepers et al. concluded in their review that these studies on the use of NIV in patients with ALS differ considerably in design and endpoint definitions and that well-designed randomized controlled trials are, to their opinion, not available [5].

We agree with the notion that more well-designed studies are needed on the effect of chronic ventilatory support in relation to QOL in patients with ALS. An additional point of concern is that in most studies, only the generic SF-36 has been used, while questionnaires set up specifically to assess quality of life in patients with respiratory insufficiency like the Maugeri Respiratory Failure (MRF-28) and the Severe Respiratory Insufficiency (SRI) were not used at all. Also, we believe that it is unfortunate that the previous studies did not report on outcomes like depression and anxiety, items frequently mentioned by patients with ALS.

In a randomized controlled study assessing the effect on QOL of home versus in-hospital initiation of NIV in patients with a neuromuscular disorder (NMD) or thoracic cage problem, we showed an overall improvement of QOL after the start of NIV [6]. However, in this study, the effect size in separate diagnostic groups, such as ALS, was not assessed. It was, however, unique in the sense that not only the SF-36, but both the SRI and MRF-28 were used to assess QOL, as was the Hospital Anxiety and Depression Scale (HADS). By doing so, we created a

broader perspective on QOL than with only the SF-36. In the present analysis, we hypothesized that the effect of NIV on QOL in patients with ALS, as assessed by the SF-36, SRI, MRF-28 and HADS questionnaires, is different compared to patients with other reasons for need of NIV.

Methods

A post hoc analysis was performed in all patients who started with NIV, from a previously published randomized controlled trial [6]. Patients, who had been diagnosed with chronic respiratory failure due to a neuromuscular disorder (NMD) or a thoracic cage problem, were included. The study was approved by the Medical Ethics Committee of the University of Groningen, University Medical Center of Groningen, and written informed consent was obtained from all patients. Chronic respiratory failure was defined as daytime arterial carbon dioxide pressure ($PaCO_2$) >6.0 kPa (>45 mmHg). Participants started NIV at home or in the hospital in a randomized design. In line with our hypothesis and reassuringly, the results for gas exchange and QOL were not significantly different between patients who started in the hospital versus at home [7]. In the current analysis, we pooled all patients without ALS in one group and compared it to those with ALS. Gas exchange was assessed by daytime arterial blood gasses from the radial artery, and the following self-administered questionnaires were completed: SRI [8], MRF-28 [9], the SF-36 [10] and the HADS [11]. The SRI contains seven domains covering: respiratory complaints, physical functioning, attendant symptoms and sleep, social relationship, anxiety, psychological well-being and social functioning. Scores range between 0 and 100, with high sores representing better quality of life. The MRF-28 contains three domains: daily activities, cognitive function and invalidity; scores range from 0 (best) to 100 (worse). The SF-36 contains eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health completed with the physical and mental component summary score 0 (worse) to 100 (best) [12]. The HADS contains the anxiety and depression domain; scores range from 0 (best) tot 42 (worse).

Statistical analyses

Independent-sample t tests were used to test for differences in change (Δ) between groups from baseline to 6 months, and paired sample t tests were performed to assess the change within groups from baseline to 2 and 6 months. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM Statistics 22 (IBM, New York, USA).

Results

77 participants were randomized to start NIV at home or in the University Medical Center of Groningen (UMCG). For this manuscript, both groups were pooled since there were no differences between the results in both intervention arms, as per prior hypothesis. Thirty participants had ALS (grouped as ALS), the other 47 participants had a neuromuscular disease (diaphragm paralysis, myotonic dystrophy, limb girdle muscular dystrophy, facioscapulohumeral dystrophy and other) or a thoracic cage problem (kyphoscoliosis or obesity hypoventilation syndrome) (grouped as non-ALS). The baseline characteristics are presented in table 1 and show that both groups were comparable in age and gas exchange.

Table 1. Baseline characteristics.

	ALS group n=30	Non ALS group n=47
Diagnosis	Amyotrophic lateral sclerosis	Neuromuscular disease (n=42) Thoracic cage problem (n=5)
Age (yr)	59.6 ± 10.6	57.7 ± 14.7
Male (%)	66.7	53.2
$PaCO_2$ (kPa)	6.6 ± 0.8	6.6 ± 1.0
PaO_2 (kPa)	10.4 ± 0.9	9.6 ± 1.6
BMI (kg/m^2)	23.8 ± 5.2	28.9 ± 6.4
Packyears	27.8 ± 19.4	18.9 ± 14.4

Data are presented as mean ± standard deviation.
kPa: kilopascal. $PaCO_2$: partial pressure of arterial carbon dioxide. PaO_2: partial pressure of arterial oxygen. BMI: body mass index.

NIV was initiated in the ALS group a median of 427 (22–2582) days after being diagnosed with ALS. Median survival in the ALS group after the initiation of NIV was 461 (220–1451) days; none of the participants was still alive at the moment of our investigation. Eight patients in each group withdrew during follow-up, mainly due to worsening of their disease, death or noncompliance with NIV [7]. Both groups showed an improvement in arterial and transcutaneous CO_2 and O_2, after 2 and 6 of NIV (Table 2); however, the mean improvements in arterial and transcutaneous CO_2 were not significantly different between the groups.

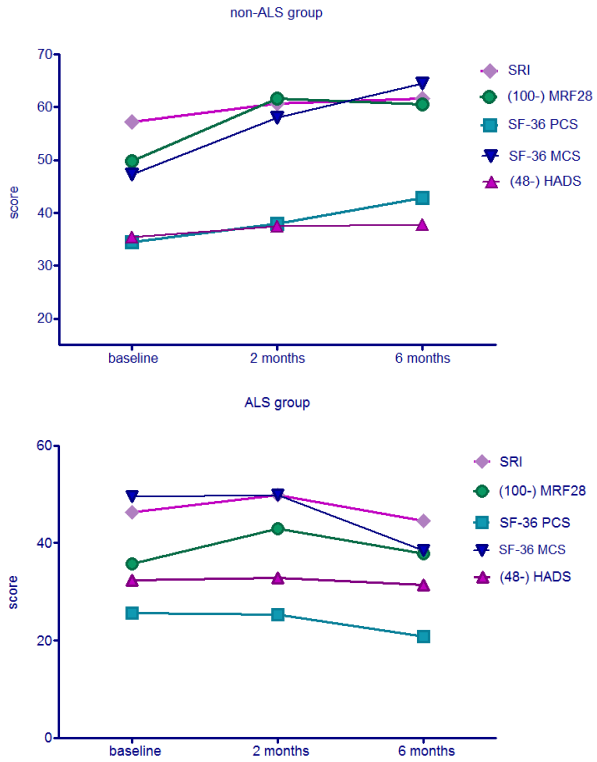
Table 2. Changes in daytime arterial blood gasses, lung function, hours of non-invasive ventilation and transcutaneous carbon dioxide and oxygen saturation after the start of non-invasive ventilation.

	ALS group			Non-ALS group			Between groups
	Baseline N=30	**Change 0-2 months N=12**	**Change 0-6 months N=19**	**Baseline N=47**	**Change 0-2 months N=17**	**Change 0-6 months N=34**	**P value for difference in change 0-6 months**
$PaCO_2$ (kPa)	6.6 ± 0.8	-1.2 ± 0.4*	-0.7 ± 0.3*	6.6 ± 1.0	-1.1 ± 0.2*	-0.7 ± 0.2*	0.862
PaO_2 (kPa)	10.4 ± 0.9	1.8 ± 0.7*	0.3 ± 0.4	9.6 ± 1.6	0.3 ± 0.7*	1.3 ± 0.3*	0.035¶
FVC (% pred)	41.6 ± 13.7	-	-9.8 ± 3.7*	45.2 ± 16.6	-	2.5 ± 2.1	0.005¶
FEV1%FVC	88.1 ± 13.8	-	-3.2 ± 3.4	76.2 ± 12.3	-	3.0 ± 2.9	0.247
	NIV initiated N=28	**N=27**	**N=23**	**NIV initiated N=46**	**N=43**	**N=42**	
Hours NIV	7.7 ± 3.8	3.5 ± 1.3*	3.8 ± 1.5*	6.8 ± 1.7	0.9 ± 0.4*	1.1 ± 0.4*	0.031¶
$tcpCO_2$ (kPa)	6.5 ± 0.9	-1.6 ± 0.3*	-2.5 ± 0.4	6.4 ± 0.9	-1.5 ± 0.2*	-1.7 ± 0.3*	0.111
$tcSpO_2$ (%)	95.9 ± 1.5	3.3 ± 0.4	3.8 ± 0.5*	95.1 ± 1.7	6.1± 1.0*	6.0 ± 1.1*	0.103

Baseline data are presented mean ± standard deviation.
Change over time are presented as mean ± standard error of mean
¶ = $p < 0.05$: for difference in change between groups 0-6 months
* = $p < 0.05$ for chances within groups from baseline
kPa: kilo Pascal. $PaCO_2$: partial pressure of arterial carbon dioxide. PaO_2: partial pressure of arterial oxygen. FVC: forced vital capacity. FEV_1: forced expiratory volume in one second. %pred: % predicted. NIV non-invasive ventilation. $tcpCO_2$: transcutaneous carbon dioxide. $tcSpO_2$: transcutaneous oxygen saturation.

The mean improvement in PaO_2 after 6 months was significantly lower in the non-ALS group compared to the ALS group. The mean number of hours on NIV increased over time in both groups. The ALS group used NIV for more than 11 h after 6 months and the other group 8 h per day (between group difference in change after 6 months $p = 0.03$). Some patients used NIV 24 h per day, depending on the progression of their disease. Forced vital capacity (FVC) showed a significant difference between both groups after 6 months as in the ALS group, the FVC decreased significantly, whereas the FVC in the non-ALS group improved slightly (Table 2). At baseline, quality of life was higher in the non-ALS group than in the ALS group. Compared to the non-ALS group, the ALS group showed significantly less improvement after 6 months on the MRF-28 total score. (Fig. 1; Table 3).

Figure 1. Change in quality of life; 2 and 6 months after starting chronic ventilatory support.



ALS: amyotrophic lateral scleroses. NIV: non-invasive ventilation.
SRI: Severe Respiratory Insufficiency (0 = worst possible health; 100 = best possible health)
MRF-28: Maugeri Respiratory Failure (0 = best possible health; 100 = worst possible health)
SF-36: Short-Form Health Status Survey (0 = worst possible health; 100 = best possible health)
SF-36 PCS, physical component score; SF-36 MCS, mental component score
HADS: Hospital Anxiety and Depression Scale (0 = best possible score; 48 = worst possible score)

Table 3. Changes in quality of life measurements after the start of non-invasive ventilation.

	ALS group			Non-ALS group			Between groups
	Baseline N=29	Change 0-2 months N=26	Change 0-6 months N=22	Baseline N=47	Change 0-2 months N=41	Change 0-6 months N=43	P-value for difference in change 0-6 months
SRI							
Respiratory complaints	42.0 ± 16.8	6.7 ± 3.0*	2.0 ± 4.2	51.9 ± 19.5	9.7 ± 2.0	7.3 ± 2.0*	0.194
Physical functioning	21.0 ± 18.4	-3.0 ± 2.8	-7.9 ± 4.5	40.0 ± 19.7	2.9 ± 2.1	1.8 ± 3.0	0.075
Attendant symp. Sleep	49.5 ± 14.6	15.2 ± 3.4*	15.6 ± 4.1*	53.3 ± 21.3	6.5 ± 2.3	11.4 ± 2.5*	0.363
Social relationship	68.2 ± 10.2	-0.6 ± 2.1	-6.3 ± 1.7*	70.9 ± 13.8	1.2 ± 2.0	1.3 ± 2.3	0.032¶
Anxiety	47.4 ± 12.1	6.9 ± 2.7*	-6.4 ± 4.2	59.5 ± 21.0	4.3 ± 2.5	9.0 ± 2.6*	0.002¶
Well-being	51.2 ± 17.4	1.8 ± 2.6	0.4 ± 2.8	63.5 ± 16.6	1.0 ± 2.0	-0.1 ± 1.9	0.899
Social functioning	44.5 ± 13.7	-2.7 ± 2.5	-7.1 ± 3.0*	61.5 ± 18.0	1.4 ± 2.0	1.1 ± 2.1	0.027¶
Summary score	46.3 ± 8.7	3.5 ± 1.8	-1.4 ± 2.4	57.2 ± 14.0	3.9 ± 1.3*	4.5 ± 1.6*	0.037¶
MRF-28							
Daily activities	74.0 ± 24.9	4.1 ± 2.4	5.4 ± 5.7	51.8 ± 29.2	-8.7 ± 3.6	-7.4 ± 4.3	0.083
Cognition	34.5 ± 33.0	-9.6 ± 6.2	-4.1 ± 6.2	37.8 ± 34.9	-9.7 ± 4.6*	-7.6 ± 4.8	0.675
Invalidity	73.1 ± 31.7	-2.3 ± 6.0	2.7 ± 5.8	44.2 ± 35.1	-2.9 ± 5.0	4.2 ± 5.5	0.867
Total score	64.2 ± 17.9	-4.7 ± 2.4	-1.4 ± 4.2	50.2 ± 22.1	-13.0 ± 2.9*	-11.9 ± 2.9*	0.041¶
HADS							
Depression	8.3 ± 7.2	-0.2 ± 0.6	1.0 ± 0.6	6.3 ± 3.8	-1.3 ± 0.4*	-1.6 ± 0.4*	0.001¶
Anxiety	7.3 ± 4.3	0.2 ± 0.6	0.8 ± 0.7	6.3 ± 4.0	-1.2 ± 0.5*	-1.1 ± 0.4*	0.017¶
Total score	15.6 ± 7.2	-0.0 ± 1.1	1.8 ± 1.1	12.6 ± 7.2	-2.5 ± 0.8*	-2.7 ± 0.7*	0.001¶
SF-36							
Physical functioning	10.3 ± 17.6	-1.0 ± 1.4	-7.1 ± 3.2*	18.2 ± 21.5	4.0 ± 1.3*	4.4 ± 2.0*	0.002¶
Role physical	6.0 ± 12.7	1.9 ± 4.6	-4.8 ± 3.3	19.7 ± 34.9	6.1 ± 6.0	17.4 ± 7.0*	0.036 ¶
Bodily pain	66.9 ± 25.4	-3.8 ± 5.0	-11.4 ± 7.4	64.8 ± 32.5	-0.3 ± 4.4	3.0 ± 4.1	0.071
General health	19.6 ± 13.6	-0.3 ± 3.1	-3.0 ± 2.8	37.2 ± 22.4	2.5 ± 2.6	7.6 ± 3.1*	0.031¶
Vitality	33.6 ± 17.3	3.1 ± 3.9	4.3 ± 4.0	40.4 ± 21.4	10.6 ± 3.1*	13.3 ± 2.7*	0.065
Social functioning	44.4 ± 27.7	2.9 ± 6.3	-13.6 ± 5.9*	59.8 ± 26.5	4.6 ± 3.7	11.3 ± 4.0*	0.001¶
Role emotional	59.8 ± 45.7	-1.3 ± 12.8	-14.3 ± 8.5	46.1 ± 51.3	13.0 ± 9.4	20.9 ± 9.1*	0.017¶
Mental health	64.4 ± 20.4	-0.5 ± 2.4	0.5 ± 3.2	66.2 ± 19.4	6.0 ± 2.0*	8.6 ± 2.5*	0.050
Phys. comp. summary	25.7 ± 10.2	-0.8 ± 2.3	-6.8 ± 2.4*	34.5 ± 16.7	3.1 ± 2.1	8.1 ± 2.8*	0.001¶
Mental comp. summary	49.4 ± 28.2	1.0 ± 7.6	-9.5 ± 5.3	47.2 ± 31.8	10.3 ± 5.6	16.6 ± 5.5*	0.004¶

Baseline data are presented as mean ± standard deviation.
Change over time are presented as mean ± standard error of mean
¶ = $p < 0.05$ for difference in change between groups 0-6 months,
* = $p < 0.05$ for changes within groups from baseline
SRI: Severe Respiratory Insufficiency (0 = worst possible health; 100 = best possible health)
MRF-28: Maugeri Respiratory Failure (0 = best possible health; 100 = worst possible health)
HADS: Hospital Anxiety Depression Scale (0 = best possible score; 42 = worst possible score)
SF-36: Short-Form Health Status Survey (0 = worst possible health; 100 = best possible health)

The sum score of the MRF-28, SRI, HADS and SF-36 improved significantly in the non-ALS group after 6 months, whilst in the ALS group, only the sum score of theSF-36 improved significantly after 6 months (Table 3). QOL in the ALS group even deteriorated as expressed by the sum scores of the MRF-28, SRI and HADS, leading to significant differences between groups after 6 months.
Both groups showed significant improvements on the attendant symptoms and sleep domain of the SRI which improved significantly in both groups. Within the non-ALS group, many domains improved significantly after both 2 and 6 months. By contrast, in the ALS group, only three domains of the SRI improved significantly after 2 and 6 months; only the attendant symptoms and sleep domain of the SRI was still significantly improved in the ALS group as compared to baseline. Two domains of the SRI, social functioning and social relationship, worsened significantly in the ALS group, showing also a significant difference between both groups.

Discussion

In this study, NIV was effective in improving gas exchange in both the ALS and the non-ALS group after 2 and 6 months. While NIV also clearly improved QOL in the non-ALS patients, the patients with ALS showed a different pattern. After 2 months, only three domains of the SRI questionnaire improved significantly. More importantly, quality of life became even worse in patients diagnosed with ALS as compared to the non-ALS group after 6 months of NIV.
More than 150 patients start chronic ventilatory support every year at the Department of Home Mechanical Ventilation of our hospital. Patients visit the outpatient clinic before starting chronic ventilatory support. Until now, we advised ALS patients to start chronic ventilatory support mainly based on the premise of a longer maintained QOL or even improved QOL in the randomized controlled trial of Bourke [4]. While different assessments on different moments were used, our study showed that after 2 months of NIV, QOL was maintained above 75 % of baseline in both groups. After 6 months, the domains physical functioning, role physical and role emotional of the SF-36 and physical functioning and social functioning of the SRI were under 75 % of baseline in the ALS group. Our group differs from that of Bourke et al., in that patients in the Bourke study had higher vital capacity and lower starting carbon dioxide at baseline compared to our study. In the Bourke study, there was a mean of 710 days after the first onset of weakness in any muscle before starting NIV. This suggests a similar moment of starting NIV in both studies, as the mean before the start of NIV in our study was 686 days. Our limited results in ALS were not the result of a bulbar impairment as gas exchange improved, and more importantly, only 2 out of 30 patients had a bulbar problem. Most importantly, however, we have to take into account that we did not include a control group with ALS but no NIV in contrast to Bourke, and therefore, could not assess if the NIV

group was worse compared to a control group. There were also important other differences between the Bourke study and ours in the assessment of QOL. The SRI and the MRF-28 questionnaires were specifically developed for patients with respiratory failure and, therefore, used in our study, next to the HADS and SF-36. It is remarkable to see that after 6 months of chronic ventilatory support in the ALS group, only the SRI domain attendant symptoms and sleep significantly improved. In contrast, the sum score of the SRI, MRF-28 and HADS improved significantly in the non-ALS group. We think that progression of the disease ALS is one of the reasons that most domains do not improve.

Routinely, during a house call visit after a patient with ALS has died, we ask next of kin or caregivers to share their experiences with us. In general, we are told they are satisfied with the level of care and result of the therapy, comfort during sleep and more awake during daytime. However, during the last months of their life, these benefits disappear as leakage of the mask during ventilation becomes a burden for both the patient and relatives. The sound of air leaking by the mask and the ventilator wakes everybody, and does not provide any comfort anymore. We sometimes hear relatives make the remark that after the patient has died, it was a relief to see them lying in bed without mask and ventilatory support. These facts are worthwhile to consider and should be shared with patients before the start of HMV.

A limitation of our study is that it was primarily set up as a randomized controlled trial, comparing initiation of NIV at home with an in-hospital start irrespective of diagnosis and, therefore, not to compare specifically ALS to non-ALS patients. Comparing patients with and without ALS is, from a life-expectancy perspective, imperfect and should be done with caution. To understand the results of the ALS group in a broader perspective, in a future study, patients with ALS should be randomized to receive NIV or not. However, starting a randomized controlled trial, one group with NIV and one group without, is probably, from an ethical perspective, not easy to realize, because NIV has become the cornerstone of symptom management in patients with ALS.

Second, the ALS group had a smaller size than the non-ALS group resulting in lower chance of finding significant within group results compared to the non-ALS group.

In conclusion, our study shows that NIV improves blood gasses in a wide range of patients, with or without ALS. However, in patients with ALS, QOL did not improve after 6 months of NIV relative to baseline, and some domains (social functioning, social relationship and physical functioning) even showed a significant deterioration compared to baseline.

Given the doubt we create on the results of NIV in patients with ALS, we believe that prospective studies are warranted in ALS patients with proper randomized controlled setup for this question, using disease-specific QOL questionnaires.

With regard to the other studies, we think that in our study, chronic ventilatory support was initiated in a more advanced stage of the disease. Therefore, we believe that these results raise questions about the efficacy of NIV in these specific patients, but they need to be confirmed in

a future dedicated randomized controlled trial in ALS patients using similar quality-of-life questionnaires.

Acknowledgements

We are very grateful to all the patients, their family members and the homecare professionals who kindly agreed to participate in this study and to everyone who worked on this project. We would also like to thank the members of the Data Safety Monitoring Board; Prof. Dr. J. G. Zijlstra, Prof. Dr. E. R. van den Heuvel (University Medical Center Groningen) and Mw. Drs. A. F. Meinesz for their contribution.

Conflicts of interest

This study was financially supported by the Health Care Insurance Board in the Netherlands, the University Medical Center Groningen, Vivisol Area UK & Benelux and ResMed.

Ethical standards

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Chapter 6

Data safety and monitoring board in non-industry trials: learning it the hard way

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Huib A.M. Kerstjens
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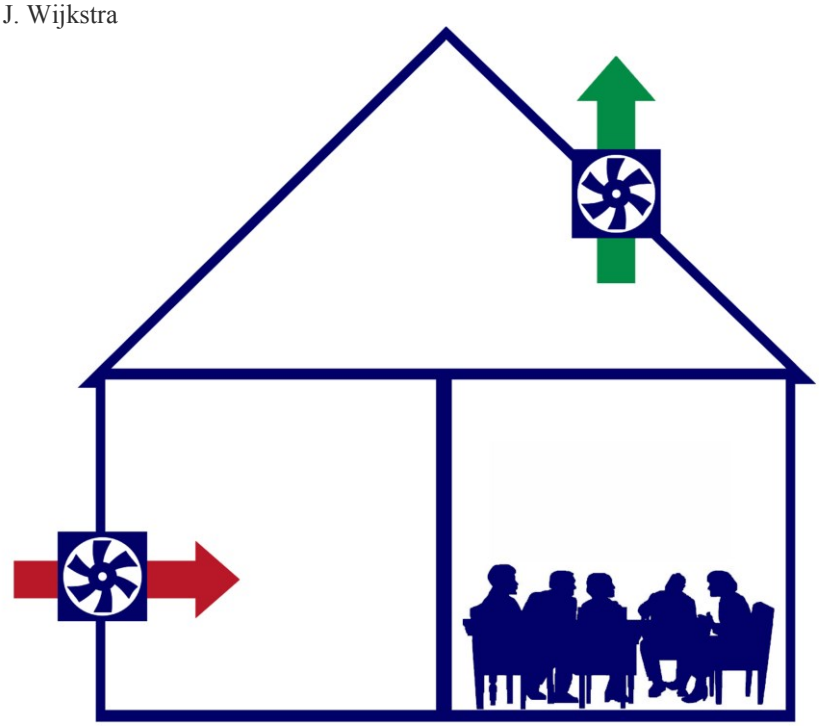

Adapted from:
Respiratory Research 2015; 16:63

Letter to the editor

In the majority of studies, no Data and Safety Monitoring Board (DSMB) is either needed or instituted. We report an investigator initiated study where we should have done this earlier than we did and discuss the lessons we learned.

The EOLUS study was a single center, randomized controlled trial of the initiation of chronic home mechanical ventilation (HMV) at home. Typical indications for HMV are neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) and Duchenne's disease next to thoracic cage deformities. The study was set up to investigate whether the initiation of HMV at home with the help of telemonitoring was not inferior to our usual in hospital start. The primary outcome measure was change in arterial carbon dioxide pressure from baseline to 6 months, for which we calculated a necessary sample size of 52 evaluable patients. The study was performed by an experienced nurse practitioner, as part of a PhD project. Weekly informal supervision was done by a senior pulmonologist and monthly progress meetings were held in a larger group. At these meetings, inclusion, lists of those excluded, and dropouts with their reasons and all deaths were discussed and minutes were always made and distributed. At four occasions over the first 14 months, a death of a patient, all with ALS, was discussed. The number of deaths occurring in this severely ill patients group, nor the circumstances were deemed remarkable. After the inclusion of 33 patients, all events were totaled and presented as such. We were shocked to realize that all 4 patients had died in the home group and none in the hospital group. The study was immediately put on hold and we reported this to the medical ethics committee. The ethics committee requested detailed reports of all cases, and an independent view from experts not involved in the study, including a statistical analysis. The conclusion of the expert group was that the four patients had died due to the progression of their ALS, without an identifiable link to the intervention. They reported no lack of effectiveness in the survivors nor safety problems. The total number of deaths was deemed within the expected rates, but non-normally distributed. The ethics committee accepted the interpretation of the expert group, and decided to restart the study, with the requirement to institute a DSMB. All future severe adverse events were to be presented to the ethics committee immediately, as were the monthly progress reports of the DSMB.

The study was subsequently finished as planned, with 77 patients randomized of which 30 with ALS. At the end, 5 patients in the home care and 2 patients in the hospital group had died, all with ALS. The hypothesis of non-inferiority of HMV institution at home with the help of telemonitoring was endorsed [1].

What did we learn? Most of all we came to fully realize that doing any study in patient groups with a high a priori risk of serious adverse events and especially of deaths, a DSMB with clear pre-set guidelines, meeting frequencies, minutes, and reporting lines to the ethics committee

should be in place. In our group, in investigator initiated studies, we had no rulings in place to see to the institution of a DSMB. We now firmly believe such a DSMB should be operational in all studies with high risk interventions. That is already frequently the case in long running pharmacy sponsored studies, and slightly less frequently in device company sponsored studies; investigator initiated studies are probably the biggest omission.
The second lesson we learned is that we should have been keen on seeing at each meeting summary tables of all events having occurred. We did discuss all deaths, but became aware of the bigger, aggregate picture later than we should have.
The DSMB consisted of a clinician expert in the field of chronic ventilation, a statistician and a clinical expert with expertise in clinical trials and methodology, all without any involvement in the conduct of the study. The DSMB evaluated the progress of the trial every four months and if necessary earlier depending on the monthly reports.
In conclusion we believe that it is of great importance that a DSMB is involved in clinical trials not only with high risk interventions but also with high a priori risk of death due to disease under study. If the DSMB had been installed from the start of our study there would have been no reason to put the study on hold. Nevertheless, we learned greatly from the events and nowadays it is mandatory in our department that clinical trials with high risk of death by the intervention or the disease, must have an actively functioning DSMB.

Competing interest

A. Hazenberg reports grants from Health Care Insurance Board in the Netherlands, grants from Vivisol Area UK & Benelux, grants from ResMed, grants from University Medical Center Groningen, during the conduct of the study. Dr. P.J. Wijkstra reports, outside this study, fees from Philips/Respironics, RESMED, VIVISOL, MedicqTEFA, Goedgebeure and Air Liquide.

Authors' contribution

AH, HAMK, PJW participated in the design and the conduct of the study, in the analysis and interpretation of the data and the draft of the manuscript. All authors approved the final manuscript

Acknowledgement

We are very grateful to all the patients, their family members and the homecare professionals who kindly agreed to participate in this study and to everyone who worked on this project. We would also like to thank the members of the Data Safety Monitoring Board; Prof. Dr. J.G. Zijlstra, Prof. Dr. E.R. van den Heuvel (University Medical Center Groningen) and Mw. Drs. A.F. Meinesz for their contribution.

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Chapter 7

Diaphragm pacing as an alternative for chronic ventilatory support

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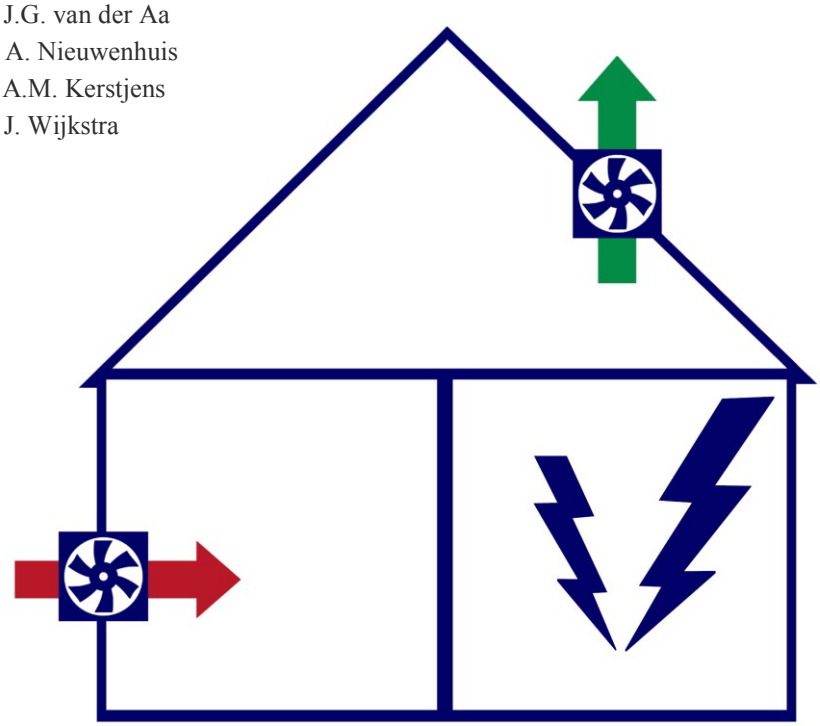


Adapted from:
Nederlands Tijdschrift voor Geneeskunde 2013;157: A5572

Abstract

Home mechanical ventilation is used for the treatment of chronic hypercapnic respiratory failure due to neuromuscular disease or thoracic cage disorder. In the majority of these patients there is an increased survival without any complications. However ventilatory support via a mask sometimes results in skin irritation, leakage and claustrophobia. In case of a tracheostomy, it can lead to increased pulmonary secretions and ulceration of the trachea. Diaphragm pacing might be an attractive alternative to prevent these complaints as it can prevent or replace the need for ventilatory support by mask or tracheostomy. Current indications are patients with spinal cord injury or with a congenital central hypoventilation syndrome. In our experience, patients can be completely or partially weaned from the mechanical ventilatory support when using a diaphragm pacer. In the Netherlands the technique is currently only performed in the University Medical Center Groningen.

Which technique?

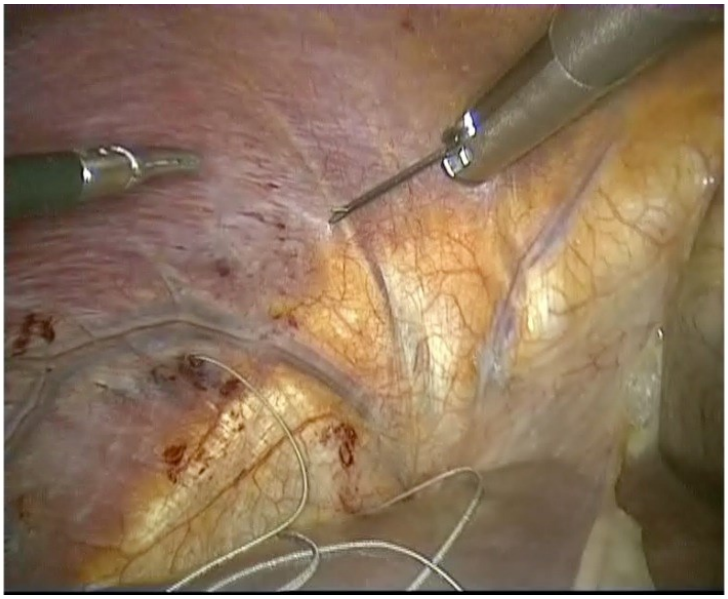
Diaphragm pacing system (DPS) is a technique in which the diaphragm is stimulated via the nervus phrenicus by an external pacemaker (figure 1).

Figure 1.

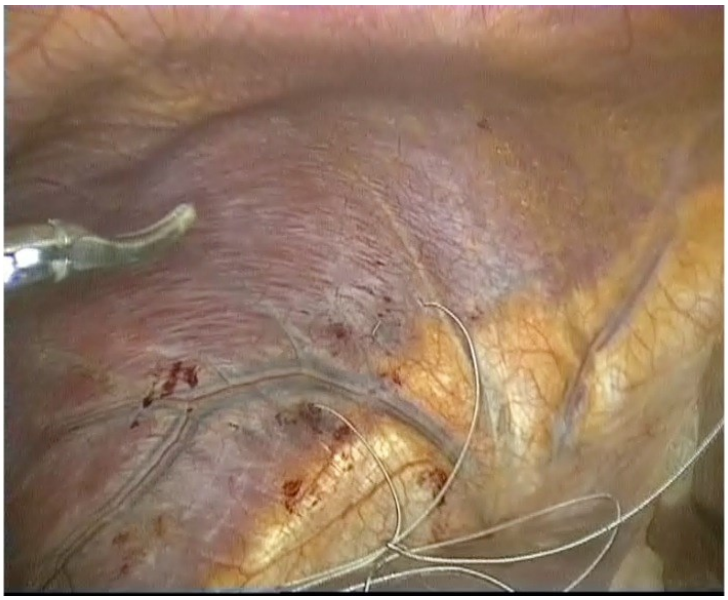
External pacer

Four electrodes, two in the left and two in the right hemi-diaphragm, are implanted via a laparoscopic approach to the caudal side of the diaphragm (figure 2) and subsequently connected to the external pacemaker [1]. A fifth neutral electrode in the abdominal wall is also connected to the pacemaker. By stimulating the diaphragm with the external pacemaker the muscle contracts and moves down allowing air to be sucked into the lungs.

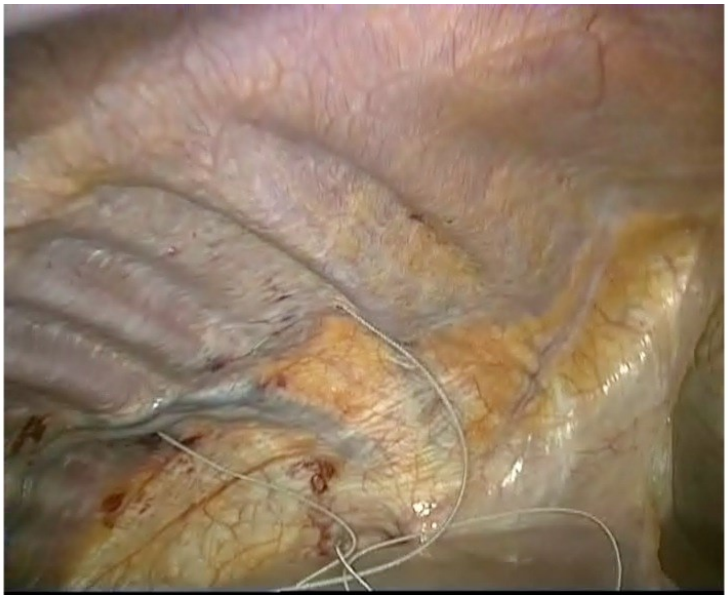
Figure 2.



A: Implementation of the electrodes via a laparoscopic approach to the caudal side of the diaphragm



B: Electrodes in the diaphragm



C: Contraction of the diaphragm after stimulation by the external pacer.

After this inspiration, exhalation follows the moment that there is no stimulus. The frequency of the pacer, the duration and the intensity of the stimulus can be adjusted, resulting in a fully controlled inspiration.

Why this new technology?

In over 2200 patients, home mechanical ventilation is applied in the Netherlands at this time. In most patients this is without complications [2]. However there are several drawbacks during non-invasieve ventilation due to skin problems, problems finding a correct fit of the mask, or patients are experiencing claustrophobia. Problems may also occur during invasive ventilation, especially due to an increase in sputum induced by the tracheostomy tube. Regular change of the tracheostomy tube may lead to ulceration, and even bleeding of the surface of the trachea. There is a constant noise from the ventilator, patients have trouble talking and sometimes there is a reduced olfactory sensation. Finally, atrophy of the diaphragm will occur prolonged loss of activity, such as with mechanical ventilation. In addition, because of the complex and expensive care in patients with invasive ventilatory support, patients have difficulty in finding a place to live.
The above mentioned problems indicate that alternatives are welcomed. DPS seems to be an attractive alternative because, depending on the underlying condition, it can replace the ventilatory support partially or completely [3].

What indications?

Patients with an indication for chronic ventilatory support due to missing or inadequate electrical stimulation of the diaphragm, such as spinal cord injury or congenital central hypoventilation syndrome may be eligible for DPS. The value in neuromuscular diseases with inadequate electrical conduction to the diaphragm, in particular in amyotrophic lateral sclerosis (ALS), is currently being investigated. DPS can only be effective if the conduction of the phrenic nerve to the diaphragm is intact from the place where it is stimulated.

What problem does this solve?

DPS is an alternative for patients who do not want to be dependent on a ventilator, mask or tracheostomy. This can be induced by skin problems and or leakage during use of a mask and the increase in sputum volume and the tendency to ulceration and bleeding in patients with invasive ventilatory support.

What is known about the effectiveness?

From March 2000 to September 2007, worldwide a diaphragm pacer was implanted in 88 patients (50 spinal cord injury and 38 ALS) [4]. Complications as pneumothorax, infection and death did not occur during the laparoscopic surgery . Immediately following the procedure, transient abdominal pain did occur occasionally. During the period of training after the implantation, some patients experienced diaphragmatic fatigue or pain projected to the shoulder. After the pacer was set properly, 98% of patients with spinal cord injury used the pacer as respiratory support and 50% of patients used it 24 hours per day. ALS patients managed to postpone the start of chronic ventilatory support sometimes with more than one year.

Within a pilot study conducted with the approval of the medical ethics committee, the University Medical Center Groningen (UMCG) included 4 patients with ALS. These four patients underwent the application of DPS without complications. The procedures went smoothly and was well accepted. Because all four patients subsequently started with non-invasive ventilation, the standard therapy, it is difficult to state with certainty anything of the effects of the DPS. Currently, the effects of DPS in patients with ALS are studied in two randomized controlled trials in England and France. In two patients with spinal cord injury, DPS was implanted in the last year. The results of DPS in these two patients were very

positive. The first patient uses invasive ventilatory support at this time only during the night (this was 24 hours per day) and uses during the day DPS. In the other patient, the nocturnal non-invasive ventilatory support was totally replaced by DPS.

How difficult is it to learn the technique?

For the implantation of the electrodes in the diaphragm, experience with laparoscopic surgery is necessary. In the first two implantations in the UMCG, the procedure was performed by an abdominal surgeon (SH) in collaboration with an American surgeon (who had done more than 100 implants). After this, the following four implantations were performed independently. After implantation, the patient follows a period of training to get used to the pacemaker gradually. Such counseling is done by a nurse from the department of home ventilation and is tailored to the specific situation of the patient in combination with the degree of dependency on ventilatory support.

Expectations for the future?

In America the Food and Drug Administration has approved DPS placement in patients with spinal cord injury and in patients with ALS. It is expected that the demand for DPS in the Netherlands will increase for patients with spinal cord injury because it provides an advantage over mechanical ventilatory support. Regarding the use of DPS in patients with ALS, we await the results of studies in England and France. Other indications are conceivable, for example double-sided diaphragm paralysis with intact conductance of the nervus phrenicus to the diaphragm, but these are still insufficiently investigated.

Where in the Netherlands?

In the UMCG, this specific technique is performed under guidance from the center of home ventilation (part of the department of pulmonary medicine and tuberculosis) in close cooperation with the abdominal surgery and anesthesiology departments. Because all patients who are eligible for DPS have chronic respiratory insufficiency and are treated by the departments of home mechanical ventilation it seems logical that these centers initiate and guide DPS. As long as the experience in the Netherlands is limited, it is wise to centralize DPS in the UMCG.

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Chapter 8

Diaphragm pacing in patients with amyotrophic lateral sclerosis

Peter J. Wijkstra
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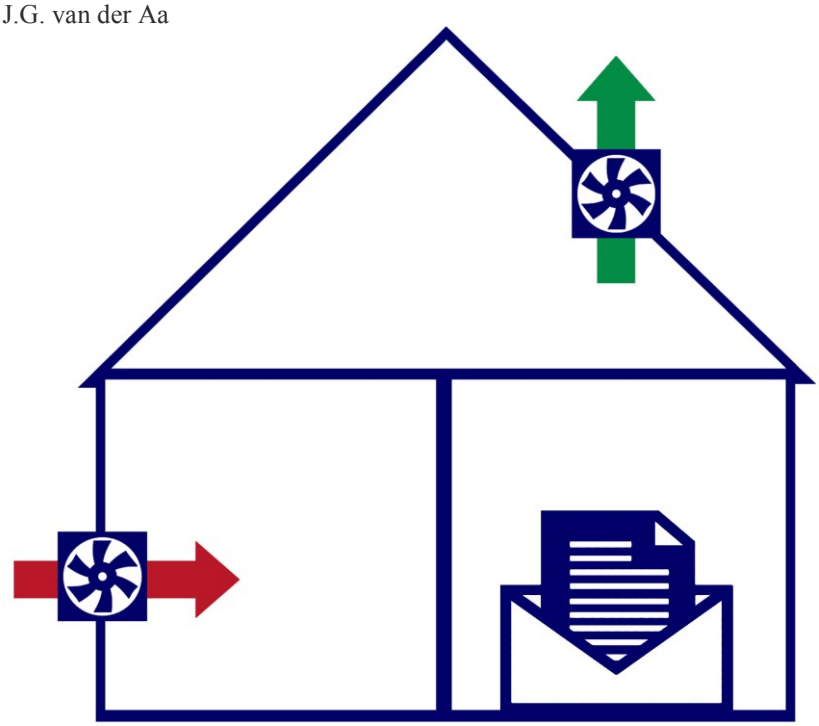

Adapted from:
The Lancet Neurology 2016; May 15 (6); 542-3

Letter to the editor

We read with great interest the report by the DiPALS Study Group Collaborators [1]. Their study showed that addition of diaphragm pacing to standard care during non-invasive ventilation was associated with decreased survival. The investigators concluded that diaphragm pacing should not be used as routine treatment for patients with amyotrophic lateral sclerosis in respiratory failure.

In the study, patients with amyotrophic lateral sclerosis were included if they had respiratory insufficiency, as determined by decline of vital capacity, impaired sniff procedure, oxygen desaturation, or hypercapnia. The latter is, by definition, a sign of hypoventilation, showing that non-invasive ventilation might be indicated. The ultimate goal of non-invasive ventilation is to improve gas-exchange. To establish whether non-invasive ventilation was effective in this trial, information about carbon dioxide, not only during daytime but also during the night, is needed. While saturation data are important, as suggested in the linked Comment on this Article [2], Christopher McDermott and co-authors did not provide any data on ventilation—ie, on carbon dioxide. The following data will help interpreting findings: baseline values of carbon dioxide and oxygen, and number of patients who were hypercapnic at baseline; carbon dioxide and oxygen during the night while on non-invasive ventilation and in patients allocated to diaphragm pacing; information on whether the diaphragm pacing system delivered adequate ventilatory support during the night; and data showing if ventilation was equally efficient in both groups of the trial.

PJW has received a fee from Synapse Biomedical to give a lecture in 2013. All other authors declare no competing interests.

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Chapter 9

Facioscapulohumeral muscular dystrophy and respiratory failure: what about the diaphragm?

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Huib A.M. Kerstjens
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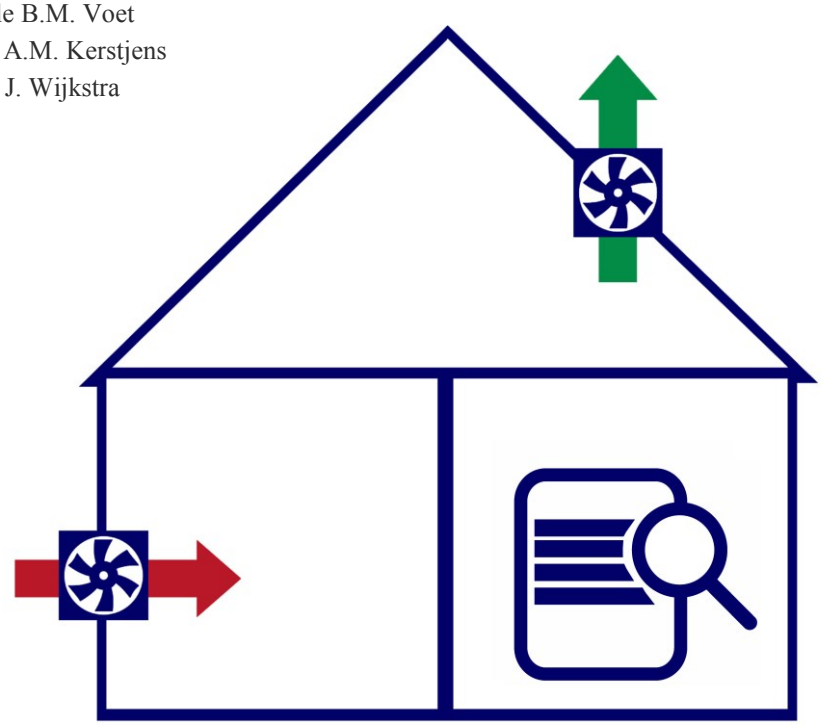


Adapted from:
Respiratory Medicine Case Report 2015; 14: 37–39

Abstract

Introduction

We present a case of facioscapulohumeral muscular dystrophy (FSHD) with a diaphragm paralysis as the primary cause of ventilatory failure. FSHD is an autosomal dominant inherited disorder with a restricted pattern of weakness. Although respiratory weakness is a relatively unknown in FSHD, it is not uncommon.

Methods

We report on the clinical findings of a 68-year old male who presented with severe dyspnoea while supine.

Results

Supplementing our clinical findings with laboratory, electrophysiological and radiological performances led to the diagnosis of diaphragm paralysis. Arterial blood gas in sitting position without supplemental oxygen showed a mild hypercapnia. His sleep improved after starting non-invasive ventilation and his daytime sleepiness disappeared.

Discussion

We conclude that in patients with FSHD who have symptoms of nocturnal hypoventilation, an adequate assessment of the diaphragm is recommended. This is of great importance as we know that nocturnal hypoventilation can be treated effectively by non-invasive ventilation.

Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant inherited disorder with a restricted pattern of weakness and is the third most common form of dystrophy [1]. In over 95% of the patients a deletion of a 3.3 kb tandem repeat, D4Z4, on chromosome 4q35 is present (FSHD type 1). In some cases (FSHD type 2), D4Z4 chromatin relaxation and stable double homeobox (DUX4) expression occur in the absence of D4Z4 array contraction [2]. FSHD type 1 and 2 are clinically characterized by asymmetric involvement of muscles in the facial, upper extremity, trunk and lower extremity region with variable severity (Table 1).

Table 1. Ricci score, muscle strength was evaluated by using the Manual Muscle Testing Scale [3].

0.5	Facial weakness
1	Mild scapular involvement without limitation of arm abduction; no awareness of disease symptoms is possible
1.5	Moderate involvement of scapular and arm muscles or both (arm abduction > 60° and strength ≥ 3 in arm muscles); no involvement of pelvic and leg muscles
2	Severe scapular involvement (arm abduction < 60° on at least one side); strength < 3 in at least one muscular district of the arms; no involvement of pelvic and leg muscles
2.5	Tibioperoneal weakness; no weakness of pelvic and proximal leg muscles
3	Mild weakness of pelvic and proximal leg muscles or both (strength ≥ 4 in all these muscles); able to stand up from a chair without support
3.5	Moderate weakness of pelvic and proximal leg muscles or both (strength ≥ 3 in all these muscles); able to stand up from a chair with monolateral support
4	Severe weakness of pelvic and proximal leg muscles or both (strength < 3 in at least one of these muscles); able to stand up from a chair with double support; able to walk unaided
4.5	Unable to stand up from a chair; walking limited to several steps with support; may use wheelchair for most activities
5	Wheelchair bound

Although respiratory weakness is a relatively unknown feature of FSHD, it is not uncommon; one study reported that almost all of the patients will develop restrictive lung disease and 10–20% will suffer from pulmonary complications (Table 2).

Table 2. Main clinical findings [1].

Respiratory symptoms of hypoventilation	Hypercapnia Dyspnoea while in supine position Fatigue Morning head age
Neuromuscular symptoms	Facial muscle weakness Shoulder girdle weakness Abdominal muscle weakness Lower-extremity muscle weakness
Extramuscular symptoms	High-frequency hearing loss Retinal telangiectasias Atrial arrhythmias Pain

Patients with FSHD may become respiratory insufficient if they have progressive weakness of respiratory muscles and/or a scoliosis, most likely when there are other signs of functionally severe impairment such as the need to use a wheelchair [4]. In this case report we present a patient with FSHD who had a diaphragm paralysis as the primary cause of ventilatory failure. He was treated successfully with non-invasive positive pressure ventilation.

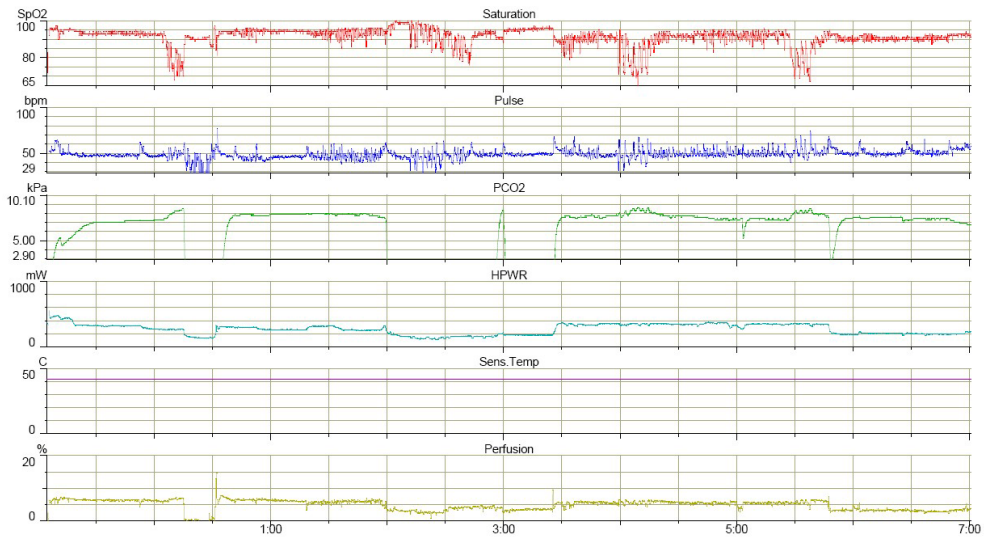
Case report

In 2008, at the age of 68, this man was diagnosed with Facioscapulohumeral muscular dystrophy (FSHD) type 1 (5 units 4A161). His medical history mentioned also psoriasis, high blood pressure for which he used bisoprolol, irbesartan, methotrexate and folate. He had also undergone surgery for penis carcinoma. His first complaints of muscle weakness were noticed at the age of 20 during a physical exam test. Exercise tolerance had been decreasing over the last 3–5 years. The last year he experienced severe dyspnoea when lying in supine position. He was referred to our hospital to evaluate his respiratory impairment. Normally he slept from 11 PM till 7 AM, did not snore and because of breathlessness in supine position he preferred to sleep on his side with the top of the bed in uplift position. In the morning he woke up reasonably fit without a headache. During daytime he experienced fatigue and sleepiness, as do many FSHD patients [5,6], and he had to take a nap every afternoon.

The patient could still walk a short distance and up a flight of stairs, but this caused shortness of breath, and a mild tachypnoea.

On physical examination, his weight was 97 kg, length 1.79 m, Body Mass index 29.7 kg/m^2. He could not lift his arms above shoulder height. There was atrophy and muscle weakness of proximal as well as distal upper and lower extremities, back and abdominal muscles, but no signs of scoliosis. The Ricci score for clinical severity of FSHD was 3 [3]. Resting heart rate: 70 beats/minute and resting respiratory rate 18 breaths/minute. In supine position there was paradoxical abdominal breathing and his respiratory rate increased. Arterial blood gas in sitting position without supplemental oxygen: acidity level (pH) 7.41, partial pressure of arterial carbon dioxide ($paCO_2$) 6.1 kilopascal (kPa), partial pressure of oxygen (paO_2) 9.7 kPa, bicarbonate (HCO_3) 28.6 mmol/l, oxygen-saturation 95%. Nocturnal registration with the TOSCA® transcutaneous monitor, before starting the chronic ventilatory support, showed a mean transcutaneous carbon dioxide ($tcpCO_2$) of 7.8 kPa (4–6 kPa is normal) and a mean oxygen saturation (SpO_2) of 91% (>92% is normal) [7]. The lowest saturation was 65% (Fig. 1).

Figure 1.



Nocturnal transcutaneous registration of carbon dioxide (mean 7.8 kPa) and oxygen saturation (mean 91%) before starting ventilation.

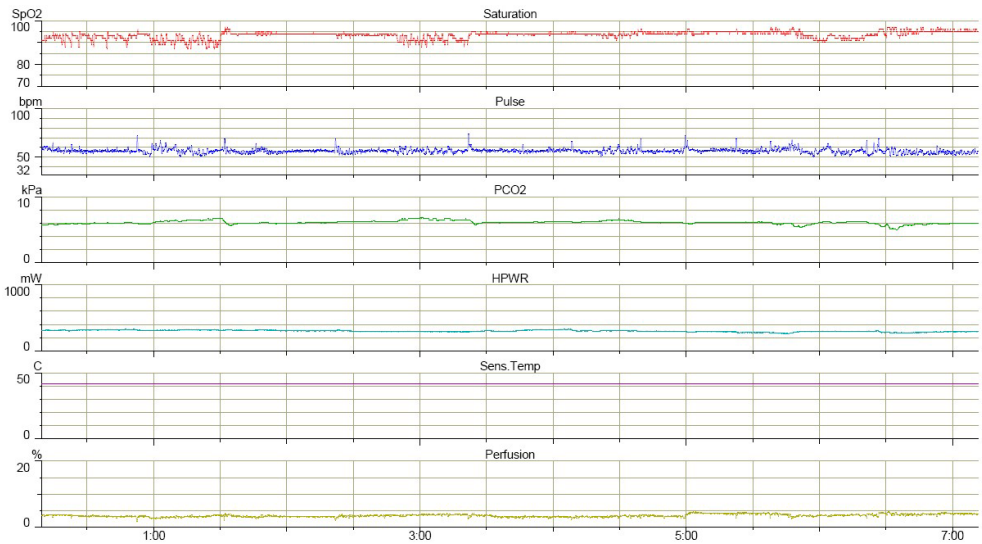
To exclude that the patient had an obstructive sleep apnoea syndrome a polysomnography (PSG) was performed [5,8,9]. The PSG showed a disturbed sleep with short awakenings and an apnoea/hypopnoea index of 2/hour (<5 is normal). Pulmonary function tests showed a decline

in forced vital capacity (FVC) of 1.5 L when moving from sitting to supine position: FVC sitting 2.60 L (59% predicted), in supine position 1.10 L (25% predicted). Fluoroscopy of the diaphragm in supine position during a sniff maneuver revealed paradoxical diaphragm movement on both sides.

Results

To relieve his physical complaints and improve his alveolar hypoventilation he started non-invasive positive pressure ventilation (NIPPV) during the night. The ventilator was set in the pressure assisted controlled mode with an inspiratory pressure of 24 cm H_2O, a positive end expiratory pressure of 8 cm H_2O and a frequency of 15 per minute. The patient used the ventilator every night with a mean usage of 7 h per night. His relationship with the ventilator was dual; he thought of it as an enemy because he had problems accepting the necessity to be ventilated, but also as a friend because it provided him better sleep and more energy during the day. While the vital capacity did not change after starting NIPPV, the arterial blood gas during the day at rest without ventilation did improve: pH 7.41, pCO_2 5.9 kPa, pO_2 11 kPa, HCO_3 28 mmol/l, oxygen-saturation 97%. Nocturnal registration one year after starting the NIPPV showed a mean $tcpCO_2$ of 6.1 kPa and a mean SpO_2 of 94% (Fig. 2).

Figure 2.



There is a relevant improvement in carbon dioxide (mean 6.1 kPa) and oxygen saturation levels (mean 94%) during ventilatory support.

By using NIPPV the patient could now sleep in supine position. He slept better and he experienced more energy during daily activities. In addition he did not fall asleep anymore during daytime hours.

Discussion

This patient with FSHD had respiratory failure due to bilateral diaphragm paralysis as shown by the large drop in the vital capacity when changing from sitting to supine position in combination with paradoxical diaphragm movement during the sniff maneuver. A recent study concluded that the diaphragm should in principle not be paralyzed in patients with FSHD and therefore the authors did not recommend an evaluation of the diaphragm [10]. However, in that study patients were included who did not have symptoms of hypoventilation like morning headache, fatigue and daytime sleepiness, so it could be expected that the lung function was only mildly impaired. It is known that patients with FSHD can have complaints due to hypoventilation [4]. As an assessment of the vital capacity in both sitting and supine position and fluoroscopy of the diaphragm was not mentioned in that study, a paralysis of the diaphragm could have been missed as the primary cause of hypoventilation. Actual search and documentation of nocturnal hypoventilation is relevant since it can be treated effectively by NIPPV. We conclude that in patients with FSHD, who have symptoms of nocturnal hypoventilation such as morning headache, fatigue and daytime sleepiness, an adequate assessment of the diaphragm is recommended.

Author contribution to the manuscript

A. Hazenberg – writing and submitting the manuscript.
Dr. N. van Alfen – revision of the manuscript for important intellectual content.
N.B.M. Voet – acquisition and interpretation of data.
Prof. H.A.M.Kerstjens – critical revision of the manuscript for important intellectual content.
Dr. P.J.Wijkstra – final approval of the version to be submitted and supervision.

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Chapter 10

Vital capacity in lying position: important in Duchenne patients

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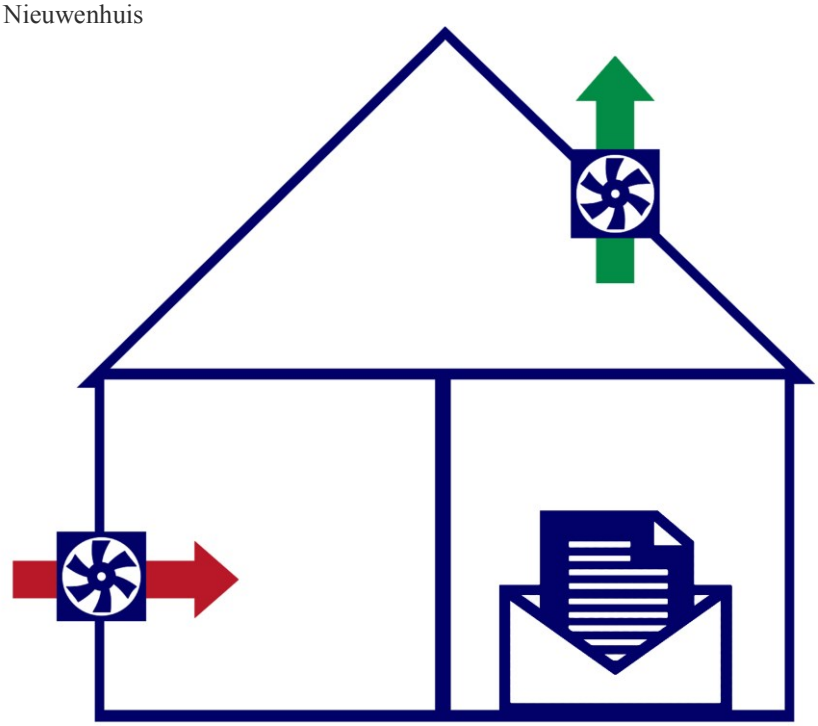

Adapted from:
European Respiratory Journal 2010; 36: 1222

To the editors

It was with great interest that we read the paper of Lo Mauro *et al*. [1] entitled "Abdominal volume contribution to tidal volume as an early indicator of respiratory impairment in Duchenne muscular dystrophy'' in a recent issue of the *European Respiratory Journal*. This paper very elegantly explained the contribution of the abdominal volume to tidal volume if patients with Duchenne disease are getting older and change from sitting to supine position. Especially in figure 6 of that manuscript, one can see very clearly the different contribution of ribcage and abdomen (diaphragm) if the patient is getting older. Despite the important contribution of this paper in this field, we would like to make two comments.

First, while the kinematic analysis was performed in both sitting and supine position, the pulmonary function tests were performed in sitting position only. This is a pity, as we know that a drop in vital capacity (VC), when a patient goes from sitting to supine position, is a sign of diaphragm paralysis. In contrast to optoelectronic plethysmography, spirometry in both positions is a simple test that can be performed in every hospital. Therefore, it would be interesting to know if the drop in the VC shows the same pattern in the different patients used in this study. For a physician taking care of these patients, it would be important to know whether he can rely on the VC in different positions to know whether the diaphragm is impaired or not.

Secondly, in this paper the assessment of nocturnal hypoxaemia is presented as clinically relevant and seems to be more pronounced in the patients with a smaller change in abdominal volume. While this might be true, the point of nocturnal hypoventilation is missed in the discussion. It was shown in the paper by Ward *et al*. [2] that nocturnal hypoventilation, with normocapnia during daytime, is an important indicator of respiratory impairment. They showed that even in these patients chronic ventilation is of benefit and should be started at this moment. Therefore the paper could have been even more informative if data on nocturnal carbon dioxide were included.

Statement of Interest

None declared.

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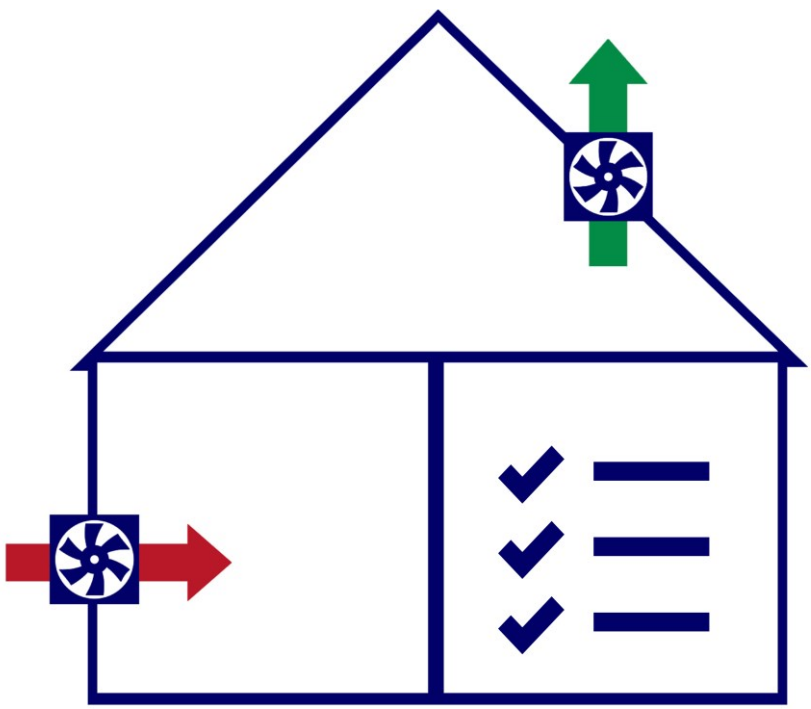
Chapter 11

Summary, general discussion and future perspectives



Summary

The aim of this thesis was to innovate the field of home mechanical ventilation primarily to see whether chronic ventilatory support can be initiated effectively outside the hospital. Different tools were used during this study and the main findings are summarized below.

Chapter 2 contains a review of home mechanical ventilation in the Netherlands over the last 2 decades. The 4 centers of home mechanical ventilation in Rotterdam, Maastricht, Utrecht en Groningen collect data every year. Patients eligible for chronic ventilatory support are those with a neuromuscular disease, thoracic cage problem, sleep disordered breathing or chronic pulmonary obstructive disease. It is remarkable to see that patients with a neuromuscular disease are still the largest group in our country, being almost 70% of the entire group, which is in contrast with the other European countries. There is a considerable, 10% annual, increase in number of patients administered on ventilatory support. The growth is specifically seen in patients treated with the non-invasive form of ventilatory support. More than 80% of patients using chronic ventilatory support lives at home. The increase in complexity of care requires strict regulation to ensure safety and seems to be best guaranteed by centers providing home mechanical ventilation to a large group of patients.

Chapter 3 shows the results of the validation of a transcutaneous carbon dioxide monitor compared with the golden standard, the arterial blood gas analysis, in adult patients with chronic respiratory failure. Paired measurements, arterial blood gasses and transcutaneous carbon dioxide, were taken in 15 patients. A maximum of 1.0 kilo Pascal difference was determined as clinically acceptable. Transcutaneous carbon dioxide measurement showed an acceptable agreement with the arterial blood gasses, during 8 hours of continuous measurement. Therefore, a transcutaneous monitor can be used to monitor carbon dioxide adequately during chronic ventilatory support.

In **chapter 4** the results of a randomized controlled trial in patients with an indication to start chronic ventilatory support are presented (EOLUS). Initiation of chronic ventilatory support is normally done in the hospital however this is expensive and often a burden to the patient. We investigated whether initiation of chronic ventilatory support at home in patients with chronic respiratory failure is non-inferior to the clinical setting. Seventy-seven patients were included, of which 38 started chronic ventilatory support at home. All patients were diagnosed with chronic respiratory failure due to a neuromuscular or thoracic cage disease. Primary outcome was the arterial carbon dioxide, while quality of life and costs were secondary outcomes. Telemonitoring was used in the home group to provide therapeutic information to the health care professional. Arterial carbon dioxide improved significantly in both groups after 6 months

of follow-up, not being inferior in the home treatment group. Quality of life in the home group, from baseline to follow-up, was not inferior compared to the hospital group. Total mean costs per patient amounted to € 726 in the home group and € 3913 in the hospital group saving more than € 3000 during home initiation of chronic ventilatory support. From a patients' perspective it is an ideal treatment as they do not have to be admitted to the hospital and their highly individualized care can be maintained during the initiation of chronic ventilatory support.

Chapter 5 displays the results of a post hoc analysis of the EOLUS study detailed in chapter 4. Discussed is whether chronic ventilatory support is really effective in patients with amyotrophic lateral scleroses (ALS). Most patients with ALS develop complaints of dyspnoea, fatigue, unrefreshing sleep and morning headache in the advanced stage of their disease due to respiratory insufficiency. Chronic ventilatory support is commonly regarded to be a treatment that is effective in reducing these complaints. Several studies have presented data regarding the effects of chronic ventilatory support on quality of life in patients with ALS. Some were positive while others produced more limitations regarding starting chronic ventilatory support in these patients, most were not randomized controlled trials. Our analysis shows that chronic ventilatory support improved gas exchange in the ALS and the non-ALS group after 2 and 6 months. While chronic ventilatory clearly improved quality of life in the non-ALS patients, the patients with ALS showed a different pattern. After 6 months of chronic ventilatory support, quality of life became worse in patients diagnosed with ALS compared to the non-ALS patients probably due to the progression of the disease ALS. However our results should be handled carefully as a control group of ALS patients not using ventilatory support was not included.

In **chapter 6** we discuss the installation of a data safety monitoring board (DSMB) in our non-industry trial. The EOLUS study (chapter 4) started without a DSMB. After the inclusion of 33 patients we noticed that 4 patients with ALS had died in the home treatment group (intervention) and none in the hospital group (control). The study was immediately put on hold and the medical ethics committee was informed. The ethics committee requested detailed reports of all cases, and an independent view from experts not involved in the study, including a statistician. Final conclusion of the expert group was that the 4 patients died due to the progression of their ALS, without an identifiable link to the intervention. If the DSMB had been installed from the start of the study there probably would have been no reason to put the study on hold. After this we realized that in this study involving patients with a high a priori risk of serious adverse events and especially of deaths an DSMB should have been installed at the start of the study. We believe this is relevant to all studies not only with high risk interventions, but also in patients with high risk of death irrespective of the intervention, as in our study. Such an DSMB is routinely installed in most industry driven studies, but perhaps not so in investigator initiated studies.

Chapter 7 describes an alternative for chronic ventilatory support; diaphragm pacing system (DPS). DPS is a technique in which the diaphragm is stimulated by an external pacemaker. By stimulating the diaphragm, the muscle contracts and moves down allowing air to be sucked into the lungs. After this inspiration, exhalation follows the moment that there is no stimulus. DPS might prevent the specific complaints associated with the use of chronic ventilatory support via a mask as skin irritation, leakage and claustrophobia and increased pulmonary secretion or ulceration of the trachea with a tracheostomy. Current indications are patients with spinal cord injury or a congenital central hypoventilation syndrome. In our experience, patients can be completely or partially weaned from the mechanical ventilatory support when using the diaphragm pacer. In the Netherlands the technique is currently only performed in the University Medical Center Groningen.

In **chapter 8** we responded to the DIPALS study, diaphragm pacing in patients with ALS. Our remark to the study is the lack of baseline data on carbon dioxide and oxygen. To be able to interpret the results of the study we would also like to see the effect of the treatment, chronic ventilatory support and diaphragm pacing, during the night. Assessment of carbon dioxide and oxygen in combination with the ventilator information can reveal whether the treatment is effective.

Chapter 9 displays a case report of a 68 year old male with facioscapulohumeral muscular dystrophy (FSHD) and respiratory failure. FSHD is an autosomal dominant inherited disorder with a restricted pattern of weakness. In supine position, the patient experienced severe dyspnoea and he experienced daytime sleepiness. The polysomnography showed a disturbed sleep with short awakenings and an apneu/hypopneu index of 2 per hour (<5 is normal). Pulmonary function tests showed a decline in forced vital capacity (FVC) of 1.5 L when moving from sitting to supine position: FVC sitting 2.60 L (59% predicted), in supine position 1.10 L (25% predicted). Arterial blood gas showed a mild hypercapnia. Fluoroscopy of the diaphragm in supine position revealed paradoxical diaphragm movement on both sides. The diaphragm paralysis was the cause of his respiratory failure. After the initiation of non-invasive chronic ventilatory support his gas exchange and sleep quality improved. We conclude that in patients with FSHD who have symptoms of nocturnal hypoventilation, an adequate assessment of the diaphragm is recommended. This is of great importance as we know that nocturnal hypoventilation can be treated effectively by non-invasive ventilation.

In **chapter 10** we point out that measuring pulmonary function in both sitting and supine position can be helpful as a diagnostic tool in patients with Duchenne muscular dystrophy. It could be a sign of diaphragm paralysis if vital capacity (VC) declines when a patient goes from sitting to supine position. Spirometry in both sitting and supine positions is a simple test that can be performed in every hospital. In addition, it is of importance to know if nocturnal

hypoventilation is present while being normocapnic during the day as this is an important indicator of respiratory impairment. When in patients with Duchenne muscular dystrophy diaphragm paralysis or nocturnal hypoventilation is present, chronic ventilatory support should be considered.

General discussion and future perspectives

The prevalence of patients on chronic ventilatory support is increasing due to more awareness for this treatment in combination with better technical options. To move forward in this fast growing group of patients with chronic ventilatory support, innovation is of importance to keep up with requests of patients and to reduce the burden to the health care system. In this chapter, all findings of the thesis will be integrated and discussed, with special focus on the implications for the clinical practice and their role in the upcoming years.

Chronic ventilatory support

The primary goal of chronic ventilatory support is to improve quality of life by reducing the signs and symptoms of chronic hypoventilation. Earlier studies showed an improvement in blood gasses after the initiation of ventilatory support [1,2]. The results of our study showed the same result with regard to the improvement in blood gasses (chapter 4).

During the inclusion period of the EOLUS study 380 patients started chronic ventilatory support of which 84 were eligible to participate. The largest group that was excluded consisted of 105 patients that were admitted to our or another hospital with an acute problem due to different diagnoses. Of the 29 patients with obesity hypoventilation syndrome only 2 participated in the study. The other 27 patients had to start ventilatory support in the hospital immediately due to an episode of acute respiratory failure. If symptoms of obstructive sleep apnoea, hypoventilation, dyspnoea, daytime sleepiness, morning headache and generalized pitting edema are present in these patients, physicians should perhaps consider initiating chronic ventilatory support earlier [3,4].

Another group of 14 patients, diagnosed with ALS, were presented at the emergency room with dyspnoea due to hypoventilation and or mucus problems. Subsequently these patients were admitted to start chronic ventilatory support immediately. These annotations indicate that for a sub group of patients the start of chronic ventilatory support in the hospital will probably remain necessary.

The second large group that was excluded consisted of 90 patients with COPD, as non-invasive ventilatory support was still not common practice in this group of patients during our inclusion period. These patients participated either in a different clinical trial or started chronic ventilatory support in combination with rehabilitation [5]. Since the evidence for starting chronic ventilatory support also in these patients with COPD, it is logical to consider initiation of chronic ventilatory support at home as well in this group.

In addition, the use of polysomnography and microchip cards with detailed ventilator information, can be of great importance in future studies to better evaluate the patient-

ventilator interactions. From a clinical perspective this is an addition that could also have a downside especially as a patient experiences an improved quality of life while being on ventilatory support. Detailed information sometimes reveals periods of inadequate patient-ventilator interaction without consequences for the effect of the treatment. So despite the fact that one is challenged to change settings of the machine, the best strategy in these patients could be “Never change a winning team”.

The effect of chronic ventilatory support on quality of life in our study population was less positive compared to previous published studies [6-10]. Probably this is due to the large number of patients with amyotrophic lateral scleroses, which was over 35% (chapter 5). We performed a post hoc analysis in the patients who started chronic ventilatory support (chapter 4). In this analysis we compared patients without ALS with those with ALS. At baseline, quality of life was higher in the non-ALS group than in the ALS group. Compared to the non-ALS group, the ALS group had significantly less improvement after 6 months of chronic ventilatory support. Based upon the results of this analysis we concluded that chronic ventilatory support improves blood gasses in patients with or without ALS. However, in patients with ALS, quality of life did not improve after 6 months of chronic ventilatory support and some domains (social functioning, social relationship and physical functioning) even showed a significant decrease compared to baseline. These results, however, should be interpreted with great care as a control group without chronic ventilatory support was not included. Follow-up of our raised question in ALS should consist of a future study with only patients with ALS, randomized to chronic ventilatory support or usual care only. In such a study quality of life should be assessed by questionnaires suitable for patients with respiratory failure the SRI and the MRF-29.

As described by Gonzalez there are two prognostic factors in patients with ALS which may indicate if chronic ventilatory support will be successful: the severity of bulbar involvement and the score of the ALSFRS-R questionnaire [11,12]. This means that we have to look at different phenotypes of ALS to select the right candidates for treatment with chronic ventilatory support.

Telemonitoring

To transfer health care from the hospital, we used telemonitoring to evaluate the initiation of chronic ventilatory support at home. Electronic data was collected from the mechanical ventilator and transcutaneous monitor, and with aid of a laptop and software specifically developed for this study, transferred to the hospital. There was a comparable improvement in blood gasses in both the home (intervention) and hospital (standard care) group, indicating that the initiation of chronic ventilatory support can be performed effectively and safely at home.

Publications related to the initiation of chronic ventilatory support outside the hospital by using telemonitoring are scarce. Chapter 4 of this thesis displays a good example of the

implementation of telemonitoring. The results of the EOLUS study shows that the use of modern technologies in patients with a chronic disease can lower the burden to the health care system as admitting them to the hospital is no longer necessary. We want to stress that the initiation of chronic ventilatory support was continued even if data was not sent to the hospital due to technical problems such as bad connection to the mobile network. In those cases a telephone call or house visit was done.

Another remarkable outcome of our results was that in the hospital group the nurse had double contact time with the patient compared to the home group. A reason could be that in the hospital it is tempting to visit a patient again if you are present on the ward. Another reason is that in the hospital often something else draws your attention, the emergency room, the outpatient clinic or a meeting with other team members which disturbs the moment you are sharing information with the patient making it less effective. At home this is quite the opposite resulting in optimal time investment for both the patient and the nurse. The visits at home took more time per visit but were less frequent than in the hospital. Future studies have to focus on which type of patient is a good candidate for home initiation.

A problem is the lack of regulation on what exactly is meant by telemonitoring, telemedicine and telehealth. Searching the internet reveals many hits but not a final conclusion of which term to use in what circumstances. Further improvements in both technical and digital possibilities in the upcoming years will facilitate the development of future e-health studies. One initiative is the HOMERUN study, a Dutch multi-center randomized controlled trial, which started May 2015. The HOMERUN study explores the national implementation of the initiation of chronic ventilatory support outside the hospital. Our aim is that in 2020 Dutch patients who are eligible for initiation of chronic ventilatory support at home can start it at home. Both health care professionals and manufactures of ventilators and transcutaneous monitors are challenged to explore all new technical and digital possibilities in order to facilitate initiation of chronic ventilatory support at home.

Transcutaneous monitoring of carbon dioxide

To initiate chronic ventilatory support outside the hospital we needed an alternative for measuring carbon dioxide in arterial blood (the golden standard). Therefore we performed a validation study of the TOSCA® transcutaneous monitor and concluded that there was an acceptable agreement with arterial blood gasses both on carbon dioxide and oxygen saturation. This means that the transcutaneous monitor can be used at home to assess gas exchange while being ventilated.

In contrast to arterial blood gasses, which is a single measurement, the TOSCA® measures continuously gas exchange while a patient uses the ventilator and therefore provides more information. By using both transcutaneous assessment and ventilator information one can monitor the ventilatory support minute by minute which is not possible with arterial blood

gasses. When in the hospital in this study, we used radial arterial lines to be able to repeat arterial blood gasses, which has the disadvantage of patients waking up or being aroused while a sample is taken, influencing the result. In our setting, to make it worse, the arterial lines were employed only at the intensive care unit making sleep even more challenging.
A recently published article concluded that transcutaneous measuring of carbon dioxide is accurate and can replace arterial samples to evaluate the effect of the chronic ventilatory support [13]. However another study showed that in patients with severe hypercapnia the difference between arterial and transcutaneous carbon dioxide increases, suggesting that its accuracy depends on the level of hypercapnia [14]. In both studies there are no remarks about the assessment in case of low levels of carbon dioxide. It would be interesting to explore this in a group of patients especially those with a neuromuscular disease, as we often see that they appreciate a low carbon dioxide level to feel comfortable.

Diaphragm paralysis

While unilateral diaphragm paralysis is often asymptomatic and is revealed by coincidence, a bilateral diaphragm paralysis is a more serious and sometimes life threatening condition. Paralysis of the diaphragm may result in dyspnoea or orthopnoea. There are different diagnostic tools to confirm that paralysis of the diaphragm is present. First, the physical exam of a patient in supine position shows paradoxical movement of the abdomen during inspiration. Diaphragm elevation can be diagnosed by chest X-ray but not its movement. Thirdly, the assessment of spirometry in both sitting and supine position can be helpfull. In supine position vital capacity shows a larger drop compared to sitting position. The sniff-test during fluoroscopy, showing no (or even paradoxical) movement of the diaphragm in supine position, should complete the diagnostic process. Some centers use ultrasound for the latter determination.
There are 3 therapeutic options in case of diaphragm paralysis:

- non-invasive ventilatory support
- plication of the diaphragm
- diaphragm pacing.

Ventilatory support can solve the problem of dyspnoea and orthopnea during the night while asleep in supine position as described in chapter 8. However, patients still complain about dyspnoea on exertion and orthopnoea while swimming or when kneeling down interfering with daily activities. In these cases plication of the diaphragm might me more effective, as it prevents paradoxical movement on inspiration. A recent study showed that tidal volume increases in combination with a decrease in ventilatory frequency after plication [15]. Despite this improvement exercise capacity remained unchanged.
Ventilatory support and plication are optional treatments in both unilateral and bilateral diaphragm paralysis.

Diaphragm pacing is currently only applicable in bilateral diaphragm paralysis and only effective if the phrenic nerve can be stimulated close to the diaphragm. Patients with an indication for chronic ventilatory support, such as spinal cord injury or congenital central hypoventilation syndrome may be eligible for diaphragm pacing. The value in neuromuscular diseases in particular in amyotrophic lateral sclerosis was also recently investigated. A randomize controlled trial was terminated, as an interim-analysis showed that patients who used the pacer died earlier compared to patients who did not used it [16]. The main conclusion of the DiPALS group was that diaphragm pacing should not be used as standard care in patients with ALS because it was associated with decreased survival. In our hospital we implanted the diaphragm pacer also in patients with ALS at the start of the introduction of this technique (chapter 7). The last years we only implanted the pacer in patients with a SCI. Some cases offered great short term results but others with were disappointing, depending on the clinical situation and mental condition of the patient.

Chronic ventilatory support, plication or pacing are all therapeutic ways to solve the patients problems. “Which is best” should be the question to be answered in future studies. Three hospitals in the Netherlands combined their experiences in treating these patients and are setting up a study to follow-up the different approaches and their outcome. The coming years we want to investigate the benefits of the different treatments in patients with an unilateral diaphragm paralysis to better understand which patients are the best candidates for which treatment.

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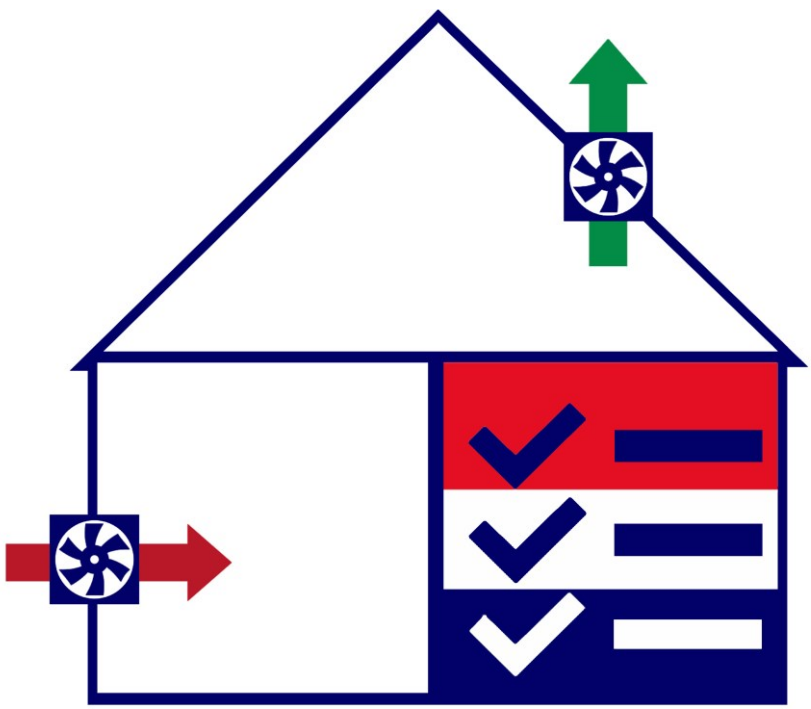
Chapter 12

Nederlandse samenvatting



Inleiding

De longen zorgen ervoor dat tijdens de inademing zuurstof in het lichaam komt en dat bij de uitademing koolzuurgas wordt uitgeademd. De belangrijkste spieren die daarbij actief zijn, zijn het middenrif en je hulpademhalingsspieren. Ademhalen doe je zonder erbij na te denken en wordt geregeld vanuit het ademhalingscentrum gelegen in de hersenen. Een effectieve ademhaling en gaswisseling is afhankelijk van een goede werking van het ademhalingscentrum, de longen, de ademhalingsspieren en een goede bewegelijkheid van de borstkas.

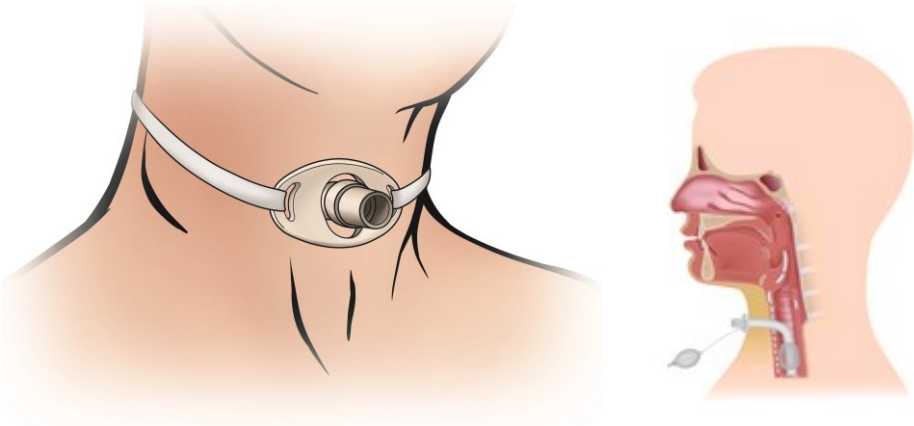
Chronische beademing in Nederland

Een patiënt die chronisch beademd wordt, is buiten het ziekenhuis afhankelijk van een beademingsapparaat om de ademhaling te ondersteunen, meestal voor de rest van het leven. Beademing wil zeggen dat de ademhaling wordt overgenomen door een beademingsapparaat. In Nederland wordt chronische beademing in de thuissituatie sinds 1960 toegepast, nadat door de poliomyelitis epidemie in de jaren 50 een grote groep patiënten langdurig afhankelijk was van een beademingsapparaat. De afgelopen jaren is het aantal patiënten met chronische beademing fors toegenomen tot bijna 3000 in 2016.

Figuur 1. Beademingsmasker.

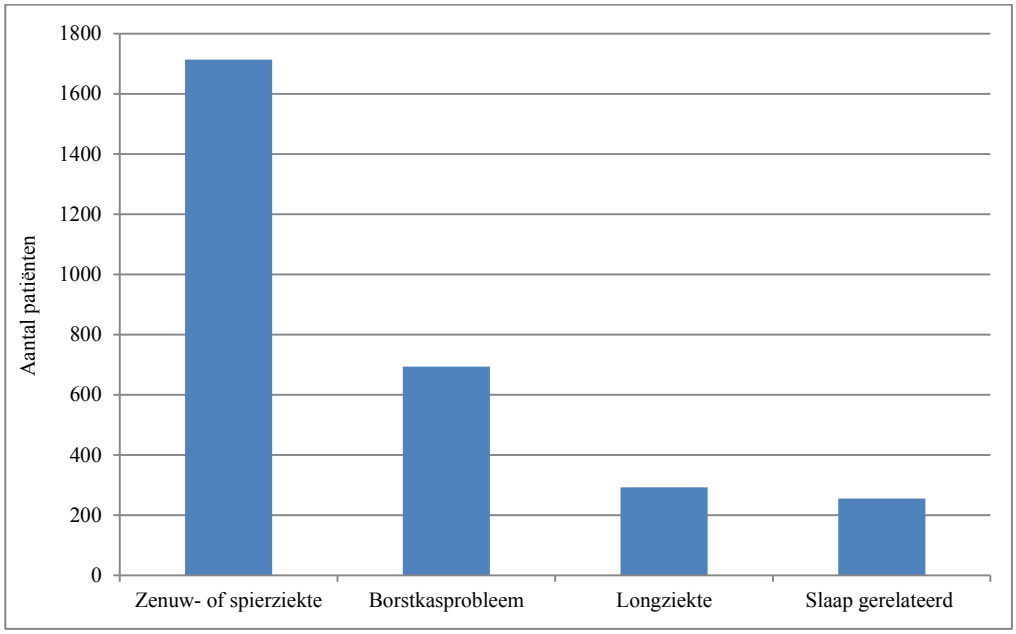
Chronische beademing lukt steeds beter via een beademingsmasker (figuur 1) waardoor het aantal patiënten dat een canule (opening via de huid in de hals naar de luchtpijp, figuur 2) nodig heeft de laatste 10 jaar is gedaald van 40% naar 19% van de totale groep met chronische beademing.

Figuur 2. Tracheostoma.



Patiënten die in aanmerking komen voor chronische beademing zijn onder te verdelen in 4 groepen (tabel 1).
De eerste groep omvat patiënten met een zenuw- en/of spierziekte. Voorbeelden zijn patiënten met spierzwakte (bijvoorbeeld ziekte van Duchenne), amyotrofische laterale sclerose (ALS), een dwarslaesie of een verlamming van het middenrif.
De tweede groep wordt gevormd door patiënten met een borstkasafwijking, bijvoorbeeld een aangeboren scheve of kromme rug. De mensen met een ademhalingsprobleem ten gevolge van overgewicht worden ook tot deze groep gerekend omdat de dikke buik het bewegen van de borstkas beperkt.
De derde groep betreft patiënten met een longziekte. In Nederland krijgen worden op dit moment patiënten met een longemfyseem (COPD) meer en meer een indicatie voor chronische beademing maar doen ook nog veel mee aan wetenschappelijk onderzoek waardoor zij ook beademing krijgen. Patiënten die op de wachtlijst staan voor een longtransplantatie, bijvoorbeeld patiënten met taai slijm ziekte, kunnen in aanmerking komen voor chronische beademing als overbrugging naar transplantatie.
De vierde groep betreft patiënten met een slaap gerelateerde ademhalingsstoornis zoals het slaap apneusyndroom waarbij de behandeling met CPAP niet effectief is.

Tabel 1.



Het belangrijkste bij chronische beademing is het verbeteren van de kwaliteit van leven door het verminderen van de klachten die vaak een gevolg zijn van hypoventilatie (te weinig ademen). Hypoventilatie, door spierzwakte of beperkte beweging van de borstkas, kan een aantal klachten veroorzaken als vermoeidheid, hoofdpijn bij het wakker worden, nachtmerries, spontane benauwdheid tijdens de nacht, concentratiestoornissen, sufheid en verminderde eetlust.

Tijdens het instellen van een patiënt op chronische beademing is het belangrijk dat wordt geprobeerd om het koolzuur- en zuurstofgehalte te verbeteren. Diverse onderzoeken hebben aangetoond dat de kwaliteit van leven verbetert na het starten met chronische beademing. Ook het sociaal en geestelijk functioneren verbetert en tegelijkertijd ook de vitaliteit, het denken en het uithoudingsvermogen. Chronische beademing heeft daarnaast een duidelijk positieve invloed op de overleving, 70% van de patiënten met de ziekte van Duchenne waren na 5 jaar nog in leven. Van de patiënten met een postpoliosyndroom was 10 jaar na het starten met chronische beademing 70% nog in leven. Door de afname van het aantal ziekenhuisopnames en de verbeterde conditie is deze behandeling ook kostenbesparend.

In Nederland wordt als regel het instellen van chronische beademing in het ziekenhuis gedaan, in een opname van bijvoorbeeld 8 dagen op een gewonde afdeling, en zelfs 2 nachten op een intensive care voor nachtelijke bloedgasregistratie. In dit proefschrift wordt onderzocht of het

instellen op chronische beademing ook buiten het ziekenhuis kan. Hiervoor zijn verschillende technieken gebruikt. De belangrijkste conclusies zijn beschreven in de volgende hoofdstukken.

Hoofdstuk 2 geeft een overzicht van de chronische beademing over de afgelopen 20 jaar. Er zijn in Nederland 4 centra voor thuisbeademing en die bevinden zich in Rotterdam, Maastricht, Utrecht en Groningen. De patiënten met een zenuw- en spierziekte zijn de grootste groep, bijna 70%. Het aantal patiënten met chronische beademing groeit elk jaar met 10%. Meer dan 80% van de patiënten met thuisbeademing verblijft thuis. Het instellen op chronische beademing is maatwerk. Het gebruik van de juiste beademingsapparatuur en van het juiste beademingsmasker of canule vraagt tijd en aandacht en is belangrijk voor een goed resultaat. De centra voor thuisbeademing kunnen door hun jarenlange ervaring op dit gebied de patiënten met de beschikbare middelen professioneel begeleiden in het ziekenhuis en de thuissituatie. De centra voor thuisbeademing bemerken de laatste jaren een toename van patiënten die complexere zorg nodig hebben. Omdat bij complexere patiënten er vaak weinig tijd per dag zonder beademing is moeten strikte voorwaarden zorgen voor een veilige situatie.

In **hoofdstuk 3** is beschreven hoe het meten van het koolzuur en zuurstof gehalte buiten het ziekenhuis kan. We hebben de gouden standaard, bloed uit de polsslagader, vergeleken met een meting via de huid met behulp van een sensor op de oorlel (transcutaan). De conclusie was dat de waarden van het koolzuur- en zuurstofgehalte bijna hetzelfde zijn als die in het bloed. Deze meting kan dus goed worden gebruikt voor het meten buiten het ziekenhuis.

Hoofdstuk 4 laat de gegevens zien van een onderzoek (EOLUS) bij 77 patiënten die moesten worden ingesteld op chronische ademhalingsondersteuning. Deze patiënten hadden een zenuw- of spierziekte of een vergroeiing van de borstkas. Loting bepaalde dat 38 patiënten thuis zijn ingesteld op de beademing en dat 39 patiënten moesten worden opgenomen in het ziekenhuis. Buiten het ziekenhuis maakten we gebruik van telemonitoring, het op afstand bekijken van gegevens van het beademingsapparaat en van de meet apparatuur. Zes maanden na het instellen op de beademing werden de gegevens van beide groepen met elkaar vergeleken. Het koolzuur- en zuurstofgehalte en de kwaliteit van leven verbeterde in beide groepen vergelijkbaar, waarmee is aangetoond dat het instellen op beademing in de thuissituatie niet alleen veilig maar ook even effectief was. Daarbij is het instellen op de beademing thuis veel goedkoper, het scheelt namelijk €3000,- per patiënt. En belangrijk, het is voor de patiënt, die thuis vaak alles heeft ingericht om zo goed mogelijk te kunnen wonen, prettig dat die niet hoeft te worden opgenomen in het ziekenhuis.

In **hoofdstuk 5** hebben we de gegevens van het EOLUS onderzoek dat is beschreven in hoofdstuk 4 nader onderzocht. Het aantal patiënten dat heeft deelgenomen aan het onderzoek vanwege de ziekte ALS, waarbij de situatie snel kan verslechteren, was meer dan 30%. De

meeste patiënten met ALS krijgen last van benauwdheid, vermoeidheid, worden niet uitgeslapen wakker, dromen eng en hebben soms hoofdpijn als de ademhalingsspieren niet meer goed werken. Beademing helpt bij het voorkomen van deze klachten en wordt wereldwijd gezien als een effectieve therapie. Na het opsplitsen van de totale groep in een ALS en niet ALS groep zagen we dat het koolzuur- en zuurstofgehalte verbeterde na 6 maanden in beide groepen. Met betrekking tot de kwaliteit van leven zagen we echter dat de ALS groep verschilde van de niet ALS groep. De ALS groep was nog wel na 2 maanden verbeterd maar niet na 6 maanden chronische beademing en dit kan heel goed komen door de snelle verslechtering van de situatie door de ziekte ALS. Het ontbreken van een controle groep (patiënten met ALS die niet beademd worden) betekent echter dat echte harde conclusies hier niet aan verbonden kunnen worden. Maar de resultaten rechtvaardigen het uitvoeren van een goed gecontroleerde studie.
Tijdens het EOLUS onderzoek zijn ook patiënten overleden. Op een gegeven moment werd het duidelijk dat in de groep die thuis werd ingesteld 4 patiënten waren overleden en nog geen enkele in de ziekenhuisgroep. Het onderzoek is toen gelijk stop gezet en er is een melding gedaan bij de medische ethische commissie van het ziekenhuis. In samenspraak is onder andere een DSMB (data safety monitoring board = gegevens en veiligheid bewakingsgroep) ingesteld om naar de resultaten tot dan toe te kijken. Na het bekijken van alle rapporten is gelukkig geconcludeerd dat het overlijden niet aan het thuis instellen lag maar aan de snelle verslechtering van de ziekte van de betrokken patiënten en mocht het onderzoek verder worden afgerond.

De DSMB met daarin 2 artsen en een deskundige op het gebeid van statistiek, die allemaal niet betrokken waren bij het EOLUS onderzoek, controleerde vanaf dat moment alle gegevens van het onderzoek en dat is beschreven in **hoofdstuk 6**. Aan het eind van de studie waren 5 patiënten overleden in de thuisgroep en 2 in de ziekenhuisgroep, hetgeen meer in balans is. De les die we hieruit geleerd hebben is dat het installeren van een DSMB altijd moet, niet alleen als de ingreep van de studie wellicht risicovol is (dat viel hier wel mee), maar ook als de patiënten die deelnemen een hoge vooraf kans hebben om te overlijden, los van de studie.

Een alternatief voor chronische beademing is beschreven in **hoofdstuk 7**. Diafragma (middenrif) pacing wordt gedaan met een pacemaker buiten het lichaam. Door middel van een kijkoperatie in de buik worden 4 elektroden op het middenrif bevestigd. Door het aanzetten van de pacemaker trekt het middenrif samen en wordt er lucht naar binnen gezogen. Als de pacemaker stopt ontspant het middenrif en ademt de patiënt weer uit. Patiënten met een hoge dwarslaesie die in aanmerking komen voor chronische beademing kunnen geschikt zijn voor middenrifpacing. Middenrifpacing kan een alternatief zijn voor patiënten die niet afhankelijk willen zijn van een beademingsapparaat met beademingsmasker of tracheacanule. Redenen

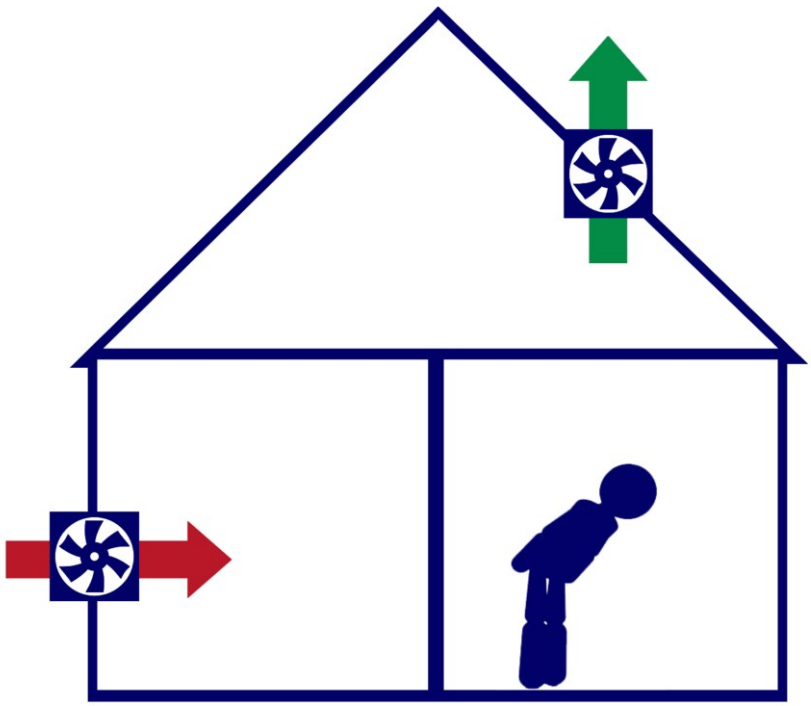
hiervoor zijn onder andere een geïrriteerde huid bij gebruik van een beademingsmasker of meer slijmproductie bij gebruik van een canule.

In **hoofdstuk 8** geven we een reactie op een onderzoek dat is gepubliceerd over diafragmapacing bij patiënten met ALS. Om de resultaten van dat onderzoek goed te kunnen bekijken hebben we gegevens nodig van het koolzuur- en zuurstofgehalte, overdag gemeten, en die zijn niet beschreven. Het gaat dan om de gegevens voor dat met de beademing is begonnen. Ook het effect van de beademing of de diafragmapacing tijdens de nacht is niet beschreven aan de hand van het koolzuur- en zuurstofgehalte aangevuld met de gegevens van het beademingsapparaat. Dit maakt het lastig is om de resultaten van het onderzoek te beoordelen.

In **hoofdstuk 9 en 10** wordt beschreven dat een middenrif verlamming ook kan voorkomen bij patiënten met een zenuw of spierziekte. Dit kan dan de reden zijn om chronische beademing te starten terwijl dan de klachten van te weinig ademen door de zenuw- of spierziekte nog niet aanwezig zijn. Door middel van een blaastest in zittende en liggende positie is vast te stellen of er een probleem aanwezig is. Bij een verlamming van het middenrif kan een patiënt in liggende positie niet zoveel lucht verplaatsen en dat is dan te zien in de uitslag van de blaastest. Na het starten met chronische beademing bij patiënten met een middenrif verlamming, verbetert de slaap en daarnaast ook het koolzuur- en zuurstofgehalte.

Chapter 13

Dankwoord



Aan het eind van van mijn promotietraject denk ik: hoe is het toch zo gekomen, van verpleegkundig specialist naar promovenda? Het begint met een idee en vervolgens word je gevraagd om te promoveren. Terugkijkend heb ik geen spijt van mijn beslissing om ja te zeggen. Ik heb de afgelopen jaren veel geleerd en ook genoten van alle bijzondere momenten en ervaringen. Het was niet altijd eenvoudig om te voldoen aan de eisen, maar het is gelukt en dat geeft veel voldoening. Het doet mij ook goed dat er een vervolg is op mijn onderzoek, de landelijke implementatie onder de naam HOMERUN. Het blijft niet in een la liggen. Dit alles was niet gelukt zonder de hulp van velen en die wil ik daarvoor bedanken. Mocht je hierna niet met naam worden genoemd, mijn dank is daardoor niet minder groot.

Allereerst wil ik alle deelnemers aan het EOLUS onderzoek bedanken. Door jullie deelname hebben we kunnen bewijzen dat het instellen op de beademing ook heel goed in de thuissituatie kan. De inzet van u als patiënt en alle hulpverleners maakte het mogelijk en heb ik als waardevol ervaren.

Promotor Prof. Dr. P.J. Wijkstra, beste Peter. Tja, waar zal ik beginnen? Je was eerst de copromotor, maar werd mijn promotor. Dat was een bijzonder moment voor ons allebei. Ook bijzonder was het vertrouwen dat je had in mijn kunnen. Terwijl ik achter het stuur zat van de Volvo, op weg naar een overleg met TNO, deed jij uit de doeken waarom jij dacht dat ik zou kunnen promoveren. In de loop van de jaren heb je me steeds vertrouwen gegeven, gezorgd dat ik de moed er in hield en zag je steeds het licht aan de horizon. Samen hebben we het een en ander bereikt zoals het binnenhalen van de ZonMw subsidie voor de landelijke HOMERUN studie en dat voelt goed. Heel erg bedankt voor alles.

Promotor Prof. Dr. H.A.M. Kerstjens, beste Huib, ook jij bent een van die bijzondere ‘ervaringen’ tijdens mijn promotie traject. De eerste overleggen dacht ik vaak: waar heeft die man het over, hoe ga ik dit ooit volgen? Dat lukte steeds beter en uiteindelijk heb ik geleerd steeds verder vooruit te denken en te anticiperen op wat me te wachten stond. Het leren tijdens het promoveren stond bij jou voorop en ik heb zeker veel van je geleerd. Ik voelde me wel af en toe wat te kort schieten, maar dat heb je nooit laten merken. Er werd dan een extra overleg gepland en dan kon ik weer verder. Ook kon je goed omgaan met een kritische noot van mijn kant en dat maakte het contact prettig. Heel erg bedankt voor de afgelopen jaren.

Het team van het Centrum voor Thuisbeademing, zonder jullie was het niet gelukt. Aaf, Anneke en Chiel, jullie werken niet meer bij de thuisbeademing, maar waren wel betrokken bij de opstart van het onderzoek. Nog bedankt voor jullie bijdrage. Jellie bedankt voor het rekruteren van de deelnemers voor het onderzoek. Altijd kon ik bij jou terecht met vragen. De overige collega’s bedankt voor jullie inzet en mocht er iemand zijn die ook wil promoveren dan sta ik er altijd voor open om mijn ervaringen met je te delen.

Dr. F.M. Verdonk-Struik, Fransien, jij bent al een tijdje klaar met je promotie en gesetteld in Zeist. Toch hebben we nog regelmatig contact en dat is altijd gezellig en waardevol. Toen we nog samen op één kamer zaten hadden we veel aan elkaar en hadden we elke dag een moment van overleg met de benen op tafel. We konden ook uren aan een stuk werken zonder te praten. Als dan op de radio onze favoriete quiz werd uitgezonden deden we beide onze oortjes in en probeerden mee te doen. De quiz eindigde altijd met: "Ladies and gentlemen, we have got ourselves a winner!". Een winnaar ben jij al een tijdje en ik nu bijna ook.

De leescommissie, bestaande uit prof. dr. J.E. Tulleken, prof. dr Y. Heijdra en prof. dr. D. Gommers, wil ik bedanken voor hun bereidheid tot het lezen en beoordelen van mijn proefschrift.

Ik wil alle co-auteurs bedanken voor hun bijdrage aan de manuscripten; dr. K.M. Vermeulen, ir. S.C.L. Prins, dr. N.A. Cobben, drs. J. Rischen, dr. N.B.M. Voet, drs. J.A. Nieuwenhuis, dr. N van Alfen, J.G. van der Aa, drs. H.S. Hofker, dr. M.J. Kampelmacher en prof. dr J.G. Zijlstra.

Tijdens mijn promotietraject zat ik in de onderzoeksgroep van de longziekten. Ook al was ik niet altijd aanwezig toch had ik het gevoel erbij te horen en te delen in de moeilijke en plezierige momenten. Zo was ik op een bruiloft, ging ik op kraamvisite en hoorde de perikelen rond het afrijden voor het rijbewijs. Ook kon ik er altijd terecht met vragen. Bedankt allemaal en we hebben het toch maar gefikst.

Collega's van de GRIAC bedankt voor de fijne samenwerking. Het was altijd inspirerend om mee te doen met de wekelijkse bijeenkomsten.

Vivisol Nederland, ResMed, Zorgverzekeraars Nederland (Menzis) en het innovatiefonds van het UMCG hebben dit onderzoek financieel ondersteund. Daarvoor hartelijk dank.

Lyanne en Sylvia, mijn paranimfen. Lyanne ken ik al mijn hele leven, ze is mijn zus. Ze werkt als verpleegkundig specialist in het Justitieel Complex Zaandam. Onze werkvelden liggen ver uit elkaar, toch hebben we raakvlakken. We kunnen daar altijd goed over praten en het levert altijd wat op. Sylvia is mijn nichtje. We startten tegelijkertijd met onze studie, zij als student geneeskunde en ik als verpleegkundig specialist, dat maakt onder andere onze band speciaal. Zij is nu huisarts en moeder.

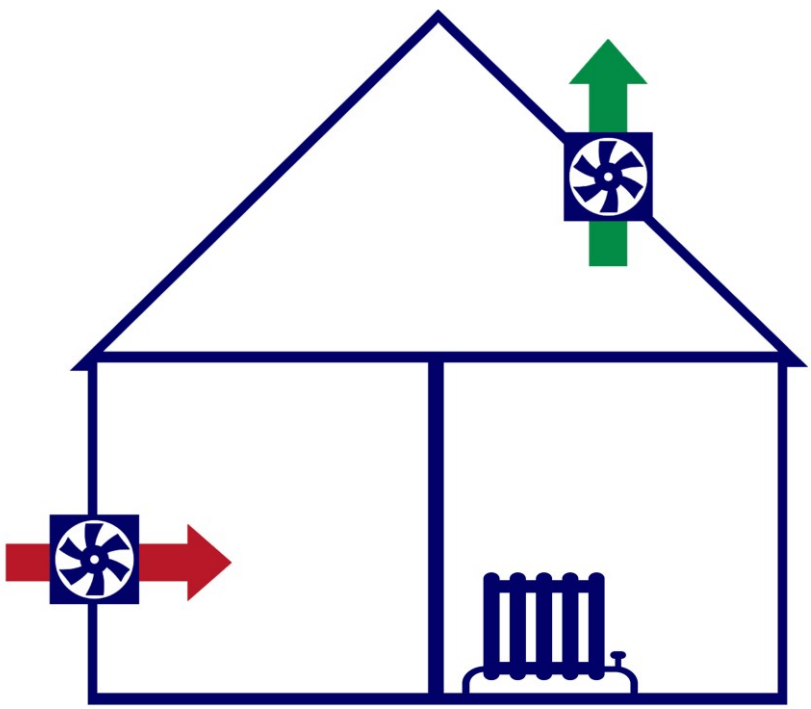
Tenslotte wil ik mijn familie en vrienden bedanken voor de steun in de afgelopen jaren. Het was een lang traject en soms voelde ik me bijna bezwaard om weer over de promotie te praten.

Toch hebben jullie altijd belangstelling getoond en zie ik het helemaal zitten om het met jullie te gaan vieren. Mijn vader en schoonvader zijn er niet bij maar zeker nog aanwezig. Mijn vader had als motto, ga de wereld in en maak er wat van. Wat zou hij er graag bij zijn geweest. Mama, mooi dat jij er bij kan zijn. Leo en Conny bedankt voor jullie steun de afgelopen jaren. Ignez, Erwin en Connie, fijn dat jullie er zijn. Moeder Nijboer, altijd in voor visite en een luisterend oor. Ria bedankt voor je belangstelling en steun en dat je alle contacten onderling zo goed weet te behouden. Pieter altijd rustig aanwezig. Tobias, Jayden en Joya bedankt voor de vrolijke noot in de afgelopen jaren.

Jans, een rustpunt in mijn bestaan, je hebt me altijd gesteund met wijze raad. Ook weet je net op het moment dat het moet me uit te dagen om weer een stap extra te doen. Ik ben heel blij dat jij er elke dag weer bent.

Chapter 14

CV



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